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Description

[0001] The present invention relates to novel benzimidazole derivatives, and, more precisely, to novel benzimidazole derivatives and their pharmaceutically acceptable salts having blood sugar level-depressing activity or PDE5-inhibiting activity. The present invention also relates to pharmaceutical compositions comprising, as an active ingredient, such benzimidazole derivatives or their salts, as well as to the use of the above benzimidazole derivatives or their pharmaceutically acceptable salts for preparing a special pharmaceutical composition, and to method of producing the above benzimidazole derivatives or their pharmaceutically acceptable salts.

[0002] EP-A-468 470 relates to special benzimidazoles, and their salts, which are said to act as angiotensin antagonists.

[0003] GB-A-2 053 215 describes defined benzimidazole derivatives, which are said to possess hypolipidaemic activity.

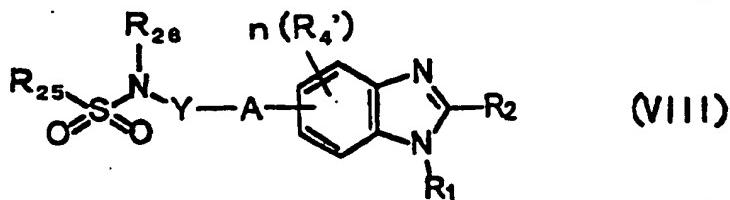
[0004] WO-A-96/16644 discloses compounds, which are said to be useful in the treatment of erectile dysfunction in male animals, including man.

[0005] In US-A-5,294,631, described are special angiotensin II receptor antagonists, which are said to be useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma.

[0006] Furthermore, US-A-5,328,919 relates to Pivaloyloxymethyl-2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof, which is said to have angiotensin II antagonistic activity and antihypertensive activity.

[0007] The subject matter of the present invention is to provide novel benzimidazole derivatives and their pharmaceutically acceptable salts, and also pharmaceutical compositions which comprise, as an active ingredient, such benzimidazole derivatives or their pharmaceutically acceptable salts, and which are useful for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

[0008] The present inventors provide pharmaceutical compositions comprising, as an active ingredient, any of benzimidazole derivatives of the following formulae (VIII) and (IX), and their pharmaceutically acceptable salts, which are usable for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.



10 In formula (VIII);

R₁ represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an aryl-lower alkyl group, a haloaryl-lower alkyloxy group, an arylsulfonylamino group, an arylcarbonylamino group, an arylcarbonyl group, an arylalkenyl group, a cyanoaryl group, and a heterocyclic group;

15 R₂ represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a halocarbonyl group, an aryl group, or a heterocyclic group;

20 R₂₅ represents an alkyl group having up to 8 carbon atoms, a lower cycloalkyl group, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

25 R₂₆ represents a hydrogen atom or a lower alkyl group; provided that, when R₂₅ and R₂₆ are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group;

30 R_{4'} represents a hydrocarbon group or a halogenated hydrocarbon group; and

n means an integer from 0 to 3,

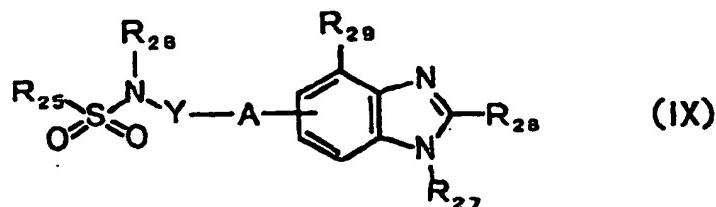
wherein the arylsulfonyl group is selected from a benzenesulfonyl group, a toluenesulfonyl group, and a naphthalenesulfonyl group;

35 the term "lower" indicates that the group has from 1 to 6 carbon atoms, unless otherwise specifically indicated; the aryl group is selected from a phenyl group and a naphthyl group, which may optionally be substituted by one or more substituents selected from a halogen atom, a lower alkyl group, a cyano group, a nitro group and a trifluoromethyl group;

40 the halo-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms;

the heterocyclic group is selected from a pyridyl group, a quinolyl group, an isoquinolyl group, a thiazolyl group, a thiadiazolyl group, a benzofuranyl group, a dibenzofuranyl group, a thianaphthalenyl group, a 1H-1,2,3-triazolyl group, a 1,2,4-triazolyl group, a tetrazolyl group, a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a pyrimidinyl group, an indolyl group, a benzimidazolyl group, which groups may optionally be substituted by one or more substituents of halogen atoms and lower alkyl groups; and

45 the lower cycloalkyl group is a cycloalkyl group having from 3 to 7 carbon atoms.



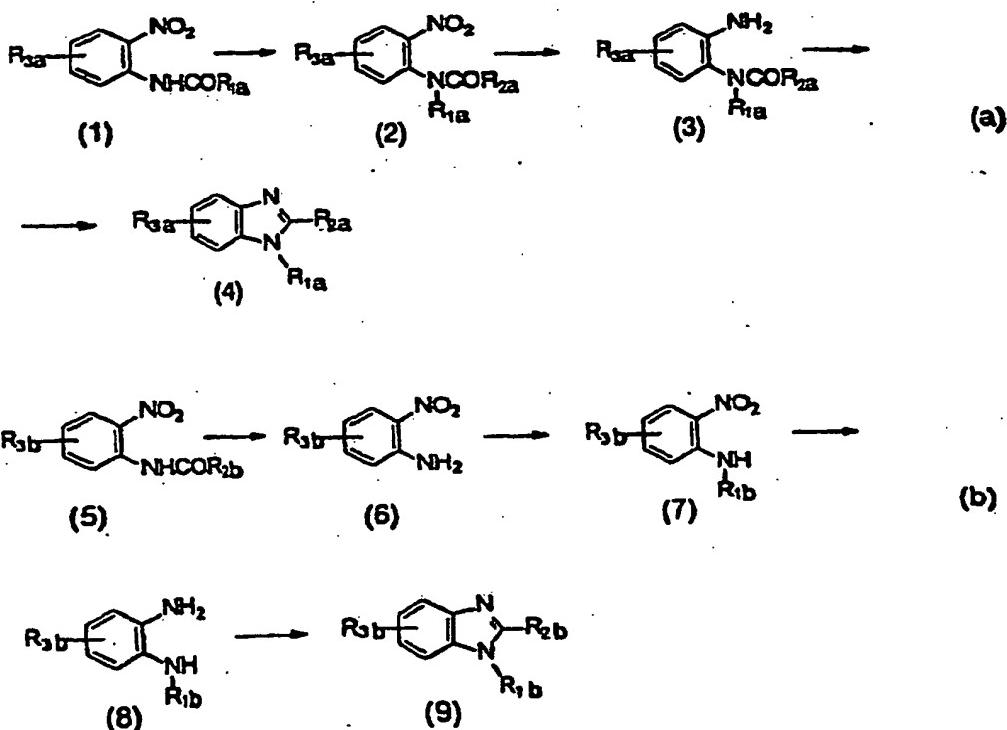
55 In formula (IX);

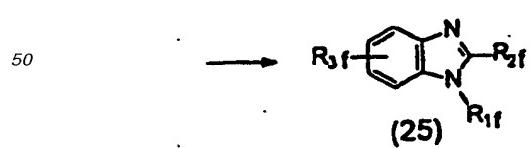
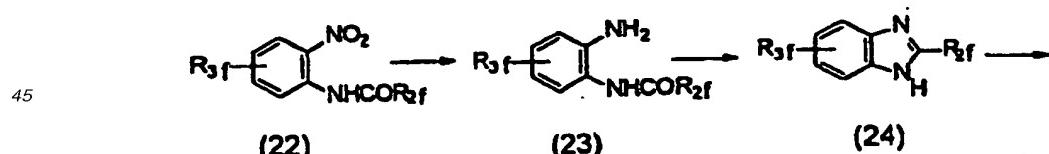
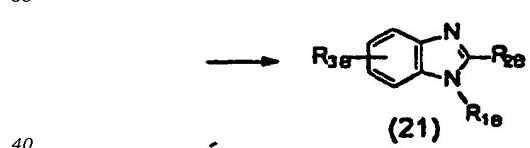
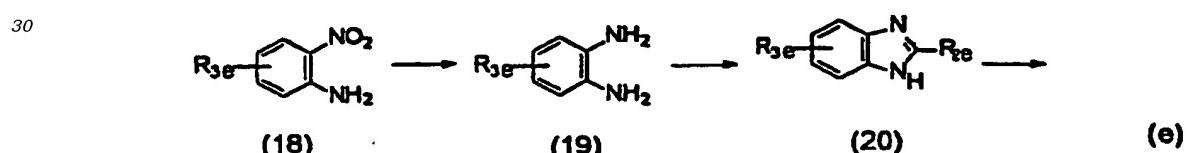
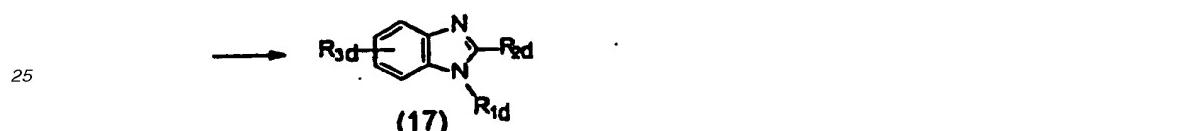
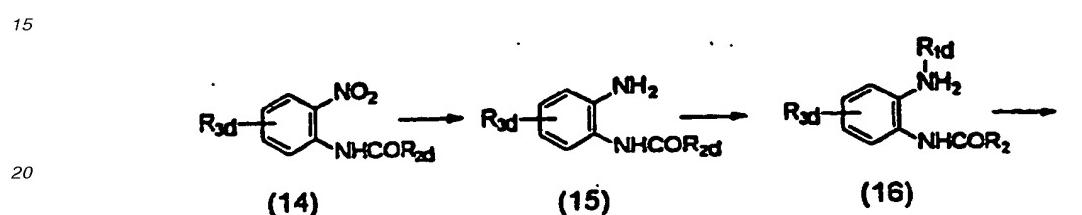
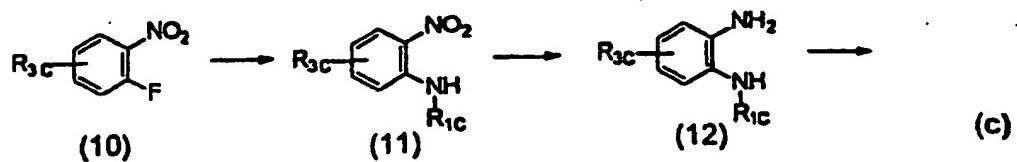
R₂₇ represents a hydrogen atom, a lower alkyl group, an arylsulfonyl group, or an aryl-lower alkyl group; wherein

the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a heterocyclic group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms; R₂₈ represents a hydrogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group; R₂₅ represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; and said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group; R₂₆ represents a hydrogen atom or a lower alkyl group; provided that, when R₂₅ and R₂₆ are both lower alkyl groups, they may be bonded together to form a ring; Y represents a carbonyl group or a lower alkylene group; A represents a single bond, or a lower alkylene or alkenylene group; and R₂₉ represents a hydrogen atom or a lower alkyl group.

[0009] The present invention also provides novel benzimidazole derivatives of the above-mentioned formulae (VIII) and (IX) and their salts.

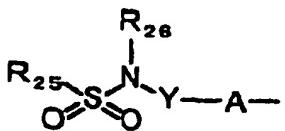
[0010] Benzimidazole derivatives to be provided by the present invention can be produced according to the following reaction formulae (a) to (f):





55 [0011] In the above-mentioned reaction formulae, R_{1a} to R_{1f} may be selected from the above-mentioned R_1 or R_{27} . R_{2a} to R_{2f} may be selected from the above-mentioned R_2 or R_{28} . The substituents R_{3a} to R_{3f} may be selected from a substituent of a formula:

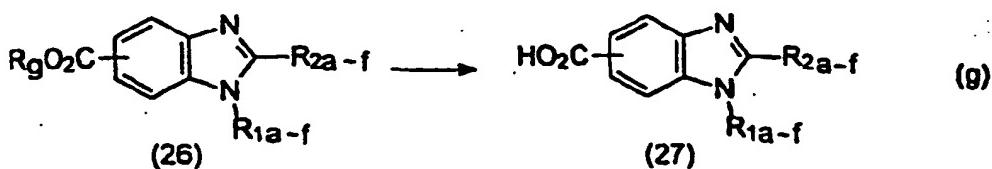
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with R₂₅, R₂₆, Y and A having the same meanings as those mentioned above. The substituents that define R_{3a}, through R_{3f} can be mutually converted to each other. For example, as in the step (g) or (h) mentioned below, the ester (26) can be converted into the corresponding acid (27) or acid halide (28). The desired benzimidazoles can be produced through the reaction of these compounds with amines or sulfonamides. It is further possible to give various derivatives, as in the step (i) or (j) or (k) or (l) or (m) or (n) mentioned below. Such conversion of the groups, R_{3a} through R_{3f} can be effected at any stage in the steps (a) through (f), while depending on the stability of R_{1a} to R_{1f} as well as R_{2a} to R_{2f} in the compounds and even on the easiness in the isolation of the products formed.

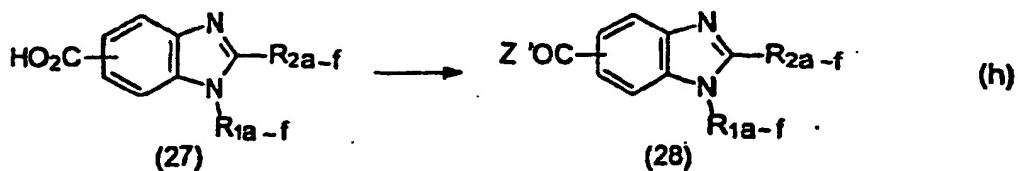
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25 [0012] In this reaction formula, R_g represents a lower alkyl group; and R_{1a-f} and R_{2a-f} have the same meanings as those mentioned above.

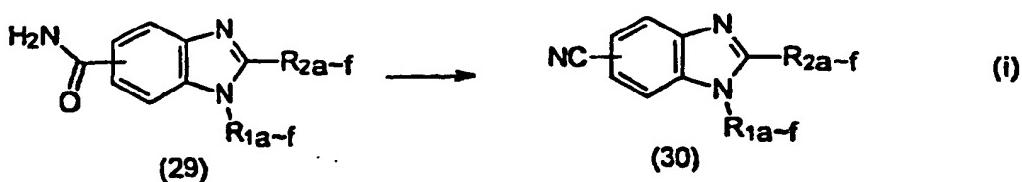
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[0013] In this reaction formula, Z' represents a chlorine atom or a bromine atom; and R_{1a-f} and R_{2a-f} have the same meanings as those mentioned above.

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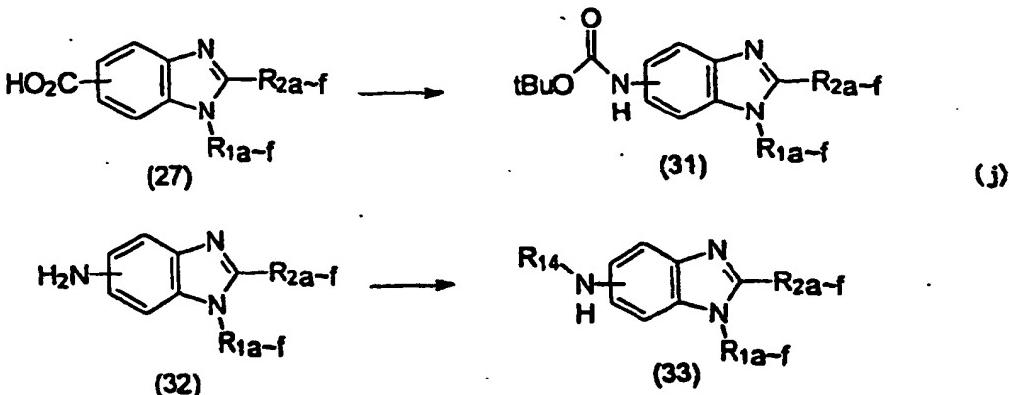


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[0014] In this reaction formula, R_{1a-f} and R_{2a-f} have the same meanings as those mentioned above.

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[0015] In this reaction formula, R_{1a-f} and R_{2a-f} have the same meanings as those mentioned above.

[0016] In the reaction step (a), a compound of formula (1) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1a}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (2). The compound of formula (2) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (3). In the process 1), the compound of formula (3) is often cyclized in the reaction system directly into a compound of formula (4). Depending on the compound of formula (2) being reduced, the compound of formula (4) may be partly formed in any of the processes 1) to 4). The compound of formula (3) may be processed with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give the compound of formula (4).

[0017] In the step (b), a compound of formula (5) may be hydrolyzed or solvolyzed with a base, such as lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, or with a carboxylic acid, a sulfonic acid or inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, into a compound of formula (6). The compound of formula (6) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1b}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (7). The compound of formula (7) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (8). A compound of formula (9) can be produced from the compound of formula (8) and the corresponding carboxylic acid or acid chloride or acid bromide or acid anhydride.

[0018] In the step (c), a compound of formula (11) can be produced from a compound of formula (10) and a compound to be represented by $R_{1c}NH_2$. The conversion of the compound of formula (11) to a compound of formula (13) is the same as that of the compound of formula (7) to the compound of formula (9) in the step (b).

[0019] In the step (d), a compound of formula (14) may be 1) reduced with a transition metal catalyst such as typically palladium, platinum, ruthenium or nickel in a hydrogen atmosphere, or 2) reduced with sodium hydrosulfite to give a compound of formula (15). The compound of formula (15) may be reacted with a base, such as lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1d}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (16). The compound of formula (16) may be treated with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give a compound of formula (17).

[0020] In the step (e), a compound of formula (18) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (19). A compound of formula (20) can be produced from the compound of formula (19) and the corresponding carboxylic acid or acid anhydride or acid chloride or acid bromide. The compound of formula (20) may be reacted with a base, such as sodium hydride, lithium diisopropylamide, lithium hydrogencarbonate, lithium carbonate, lithium hydroxide, sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydrogencarbonate, potassium carbonate, potassium hydroxide or the like, and with a compound to be represented by $R_{1a}Z$ (where Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group) to give a compound of formula (21).

[0021] In the process comprising the above-mentioned step, in general, the product may be obtained as a mixture comprising the compound of formula (21) where R_{3a} is positioned in the 5-position and that where it is in the 6-position, or a mixture comprising the compound of formula (21) where R_{3a} is positioned in the 4-position and that where it is in the 7-position. Each compound of formula (21) can be purified from the mixture as the single compound, for example, through recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like.

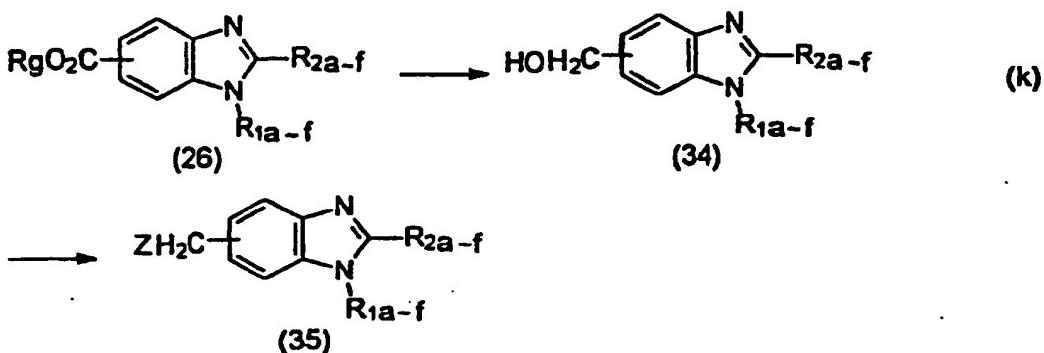
[0022] In the step (f), a compound of formula (22) may be 1) reduced with reduced iron or zinc under an acidic condition, or 2) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in a hydrogen atmosphere, or 3) reduced with a transition metal catalyst, such as typically palladium, platinum, ruthenium or nickel, in the presence of formic acid, or 4) reduced with sodium hydrosulfite, to be converted into a compound of formula (23). In the process 1), the compound of formula (23) is often cyclized in the reaction system directly into a compound of formula (24). Depending on the compound of formula (22) being reduced, the compound of formula (24) may be partly formed in any of the processes 1) to 4). The compound of formula (23) may be processed with a carboxylic acid, a sulfonic acid or an inorganic acid, such as acetic acid, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or the like, to give the compound of formula (24). The compound of formula (24) may be converted into a benzimidazole compound of formula (25) in the same manner as in the step (e) of converting the compound of formula (20) into the compound of formula (21). In this step, in general, the product may be obtained as a mixture comprising the compound of formula (25) where R_{3f} is positioned in the 5-position and that where it is in the 6-position, or a mixture comprising the compound of formula (25) where R_{3f} is positioned in the 4-position and that where it is in the 7-position. Each compound of formula (25) can be purified from the mixture as the single compound, for example, through recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography or the like.

[0023] In the step (g), a compound of formula (26) may be hydrolyzed with a base, such as lithium hydroxide, sodium hydroxide, potassium hydroxide or the like, to give a compound of formula (27). The compound of formula (27) may be reacted with a carbonyldiimidazole and then with amines or sulfonamides in the presence of a base to give different benzimidazole derivatives.

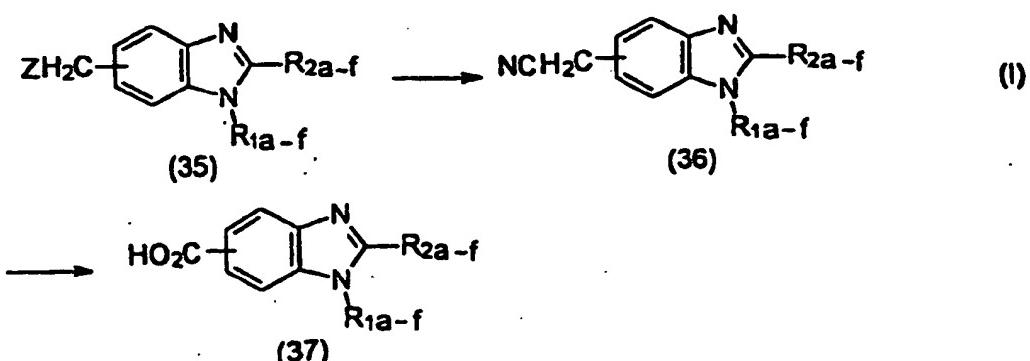
[0024] In the step (h), the compound of formula (27) may be processed with thionyl chloride or thionyl bromide or phosphorus trichloride or phosphorus pentachloride or phosphorus oxychloride to be converted into its acid halide of formula (28). The compound of formula (28) may be reacted with amines or sulfonamides to give different benzimidazole derivatives.

[0025] In the step (i), a compound of formula (29) may be reacted with titanium tetrachloride to give a compound of formula (30).

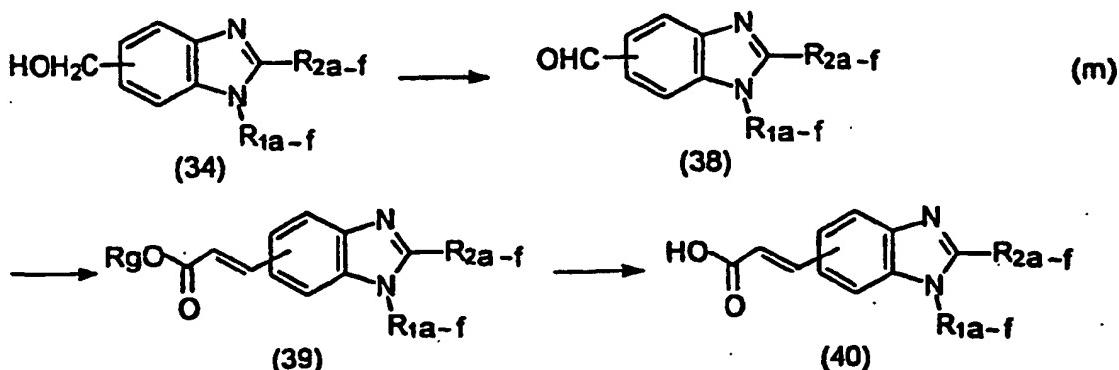
[0026] In the step (j), the compound of formula (27) may be reacted with an azide, such as typically diphenylphosphorylazide, in the presence of an alcohol, such as typically t-butanol, to give a compound of formula (31). The compound of formula (31) may be decomposed with an acid to give a compound of formula (32). The compound of formula (32) may be reacted with a compound to be represented by $R_{40}Z$ (where Z represents a chlorine atom or a bromine atom) to give a compound of formula (33).



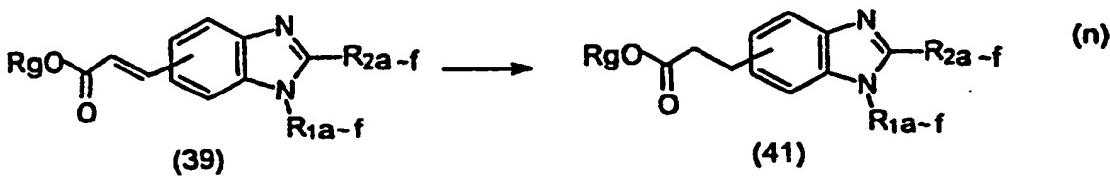
wherein R_g , R_{1a-f} , and R_{2a-f} have the same meanings as those mentioned above; and Z represents a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group.



wherein R_{1a-f} , R_{2a-f} and Z have the same meanings as those mentioned above.



wherein R_{1a-f} , R_{2a-f} and R_g have the same meanings as those mentioned above.



wherein R_{1a-f} , R_{2a-f} and R_9 have the same meanings as those mentioned above.

[0027] In the step (k), the compound of formula (26) may be reduced into a compound of formula (34), which may be then treated with thionyl chloride, thionyl bromide, phosphorus oxychloride, phosphorus oxybromide, phosphorus trichloride, phosphorus pentachloride, methanesulfonyl chloride, toluenesulfonyl chloride or the like to be converted into a compound of formula (35).

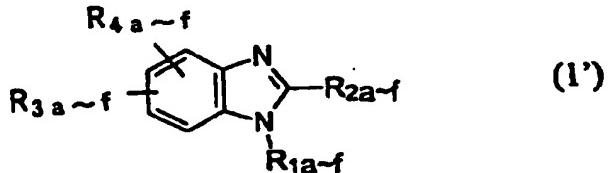
[0028] In the step (I), the compound of formula (35) may be reacted with sodium cyanide or potassium cyanide to give a compound of formula (36), which may be then hydrolyzed with lithium hydroxide or sodium hydroxide or potassium hydroxide to give a carboxylic acid of formula (37).

[0029] In the step (m), a compound of formula (38) to be obtained by oxidizing the compound of formula (34) may be reacted with an alkyl (triphenylphosphoranimidoyl)acetate to give a compound of formula (39), which may then be hydrolyzed with lithium hydroxide or sodium hydroxide or potassium hydroxide to give a carboxylic acid of formula (40).

The compound of formula (35), (37) or (40) may be reacted with amines or sulfonylamides to give different benzimidazole compounds.

[0030] In the step (n), the compound of formula (39) may be reduced with palladium, platinum, ruthenium or the like transition metal catalyst in a hydrogen atmosphere or in the presence of formic acid to give a compound of formula (41).

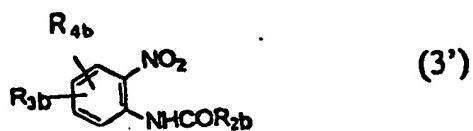
[0031] The following compounds of:



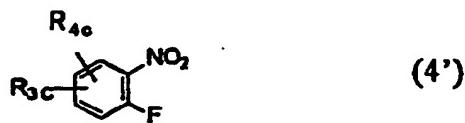
where R_{1a-f} , R_{2a-f} and R_{3a-f} have the same meanings as those mentioned above; and R_{4a-f} may be selected from the above-mentioned R_4' and R_{29} .
can be produced according to the steps (a) to (f) while starting from the following compounds of:



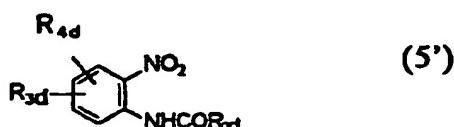
where R_{1a} , R_{2a} and R_{3a} have the same meanings as those mentioned above; and R_{4a} may be selected from the above-mentioned R_1' and R_{2a}' ;



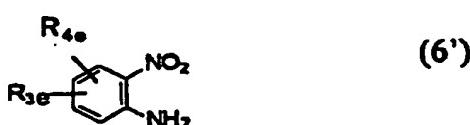
where R_{1b} , R_{2b} and R_{3b} have the same meanings as those mentioned above; and R_{4b} may be selected from the above-mentioned R_4 ' and R_{29} ;



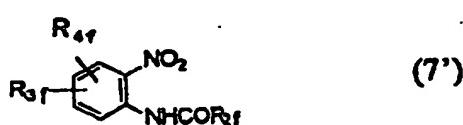
where R_{1c}, R_{2c} and R_{3c} have the same meanings as those mentioned above; and R_{4c} may be selected from the above-mentioned R₄' and R₂₉;



15 where R_{1d}, R_{2d} and R_{3d} have the same meanings as those mentioned above; and R_{4d} may be selected from the above-mentioned R₄' and R₂₉;



25 where R_{1e}, R_{2e} and R_{3e} have the same meanings as those mentioned above; and R_{4e} may be selected from the above-mentioned R₄' and R₂₉:



35 where R_{1f}, R_{2f} and R_{3f} have the same meanings as those mentioned above; and R_{4f} may be selected from the above-mentioned R₄' and R₂₉.

40 [0032] If desired, the intermediates formed in the above-mentioned steps may optionally be purified, prior to being subjected to the next step, through any conventional purification including, for example, recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. If also desired, the final products of the compounds of the present invention may optionally be purified through any conventional purification which is employed in the art of purifying organic compounds and which includes, for example, recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. To identify these 45 compounds, employable is any of NMR spectrography, mass spectrography, IR spectrography, elementary analysis, measurement of melting point and others.

[0033] Preferred embodiments and their details of various definitions as referred to herein to be within the scope of the present invention are described below.

50 [0034] Unless otherwise specifically indicated herein, the terminology "lower" indicates that the group has from 1 to 6 carbon atoms. As preferred examples of the lower alkyl group as referred to herein, mentioned are linear or branched alkyl groups including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, 55 a 3,3-dimethylbutyl group, a 1-ethyl-1-methyl propyl group, etc.

[0035] An alkyl group having up to 7 carbon atoms is a linear or branched alkyl group, including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methyl propyl group, etc.

1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, etc.

[0036] An alkyl group having up to 8 carbon atoms is a linear or branched alkyl group, including a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, an n-octyl group, a 1-methylheptyl group, a 2-methylheptyl group, a 3-methylheptyl group, a 4-methylheptyl group, a 5-methylheptyl group, a 6-methylheptyl group, a 1-ethylhexyl group, a 2-ethylhexyl group, a 3-ethylhexyl group, a 4-ethylhexyl group, a 5-ethylhexyl group, a 1,1-dimethylhexyl group, a 2,2-dimethylhexyl group, a 3,3-dimethylhexyl group, a 4,4-dimethylhexyl group, a 5,5-dimethylhexyl group, a 1-propylpentyl group, a 2-propylpentyl group, etc.

[0037] The lower alkylene group is an alkylene group having 6 or less carbon atoms, including a methylene group, an ethylene group, a propylene group, a butylene group, a pentylene group, a hexylene group, etc. The lower alkenylene group is an alkenylene group having 6 or less carbon atoms, including an ethenylene group, a 1-propenylene group, a 2-propenylene group, a 1-butenylene group, a 2-butenylene group, a 3-butenylene group, a 1-pentenylene group, a 2-pentenylene group, a 3-pentenylene group, a 4-pentenylene group, a 1-hexenylene group, a 2-hexenylene group, a 3-hexenylene group, a 4-hexenylene group, a 5-hexenylene group, etc.

[0038] The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a fluorine atom, a chlorine atom and a bromine atom.

[0039] The halo-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms selected from fluorine, chlorine, bromine and iodine atoms. Preferred is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms selected from fluorine, chlorine and bromine atoms. It includes, for example, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a chloromethyl group, a dichloromethyl group, a trichloromethyl group, a bromomethyl group, a dibromomethyl group, a tribromomethyl group, a 1-fluoroethyl group, a 1-chloroethyl group, a 1-bromoethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a 2-bromoethyl group, a 1,2-difluoroethyl group, a 1,2-dichloroethyl group, a 1,2-dibromoethyl group, a 2,2,2-trifluoroethyl group, a heptafluoroethyl group, a 1-fluoropropyl group, a 1-chloropropyl group, a 1-bromopropyl group, a 2-fluoropropyl group, a 2-chloropropyl group, a 2-bromopropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 3-bromopropyl group, a 1,2-difluoropropyl group, a 1,2-dichloropropyl group, a 1,2-dibromopropyl group, a 2,3-difluoropropyl group, a 2,3-dichloropropyl group, a 2,3-dibromopropyl group, a 3,3,3-trifluoropropyl group, a 2,2,3,3,3-pentafluoropropyl group, a 2-fluorobutyl group, a 2-chlorobutyl group, a 2-bromobutyl group, a 4-fluorobutyl group, a 4-chlorobutyl group, a 4-bromobutyl group, a 4,4,4-trifluorobutyl group, a 2,2,3,3,4,4,4-heptafluorobutyl group, a perfluorobutyl group, a 2-fluoropentyl group, a 2-chloropentyl group, a 2-bromopentyl group, a 5-fluoropentyl group, a 5-chloropentyl group, a 5-bromopentyl group, a perfluoropentyl group, a 2-fluorohexyl group, a 2-chlorohexyl group, a 2-bromohexyl group, a 6-fluorohexyl group, a 6-chlorohexyl group, a 6-bromohexyl group, a perfluorohexyl group, a 2-fluoroheptyl group, a 2-chloroheptyl group, a 2-bromoheptyl group, a 7-fluoroheptyl group, a 7-chloroheptyl group, a 7-bromoheptyl group, a perfluoroheptyl group, etc.

[0040] The lower alkoxy group is a linear or branched alkyloxy group having up to 6 carbon atoms. It includes, for example, a methoxy group, an ethoxy group, an n-propyloxy group, an i-propyloxy group, an n-butyloxy group, an i-butyloxy group, a sec-butyloxy group, a t-butyloxy group, an n-pentyloxy group, an i-pentyloxy group, a sec-pentyloxy group, a t-pentyloxy group, a 2-methylbutoxy group, an n-hexyloxy group, an i-hexyloxy group, a t-hexyloxy group, a sec-hexyloxy group, a 2-methylpentyloxy group, a 3-methylpentyloxy group, a 1-ethylbutyloxy group, a 2-ethylbutyloxy group, a 1,1-dimethylbutyloxy group, a 2,2-dimethylbutyloxy group, a 3,3-dimethylbutyloxy group, a 1-ethyl-1-methylpropyloxy group, etc. Preferred are a methoxy group, an ethoxy group, an n-propyloxy group, an i-propyloxy group, an n-butyloxy group, an i-butyloxy group, a sec-butyloxy group, a t-butyloxy group, etc.

[0041] The lower cycloalkyl group is a cycloalkyl group having from 3 to 7 carbon atoms, and preferably includes a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, etc. More preferred are a cyclopropyl group, a cyclobutyl group, etc.

[0042] The lower alkoxy-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, as substituted with a linear or branched alkyloxy group having up to 8 carbon atoms. For example, this includes a methoxyme-

thyl group, a methoxyethyl group, a methoxypropyl group, a methoxybutyl group, a methoxypentyl group, a methoxyhexyl group, a methoxyheptyl group, a methoxyoctyl group, an ethoxymethyl group, an ethoxyethyl group, an ethoxybutyl group, an ethoxypentyl group, an ethoxyhexyl group, an ethoxyheptyl group, an ethoxyoctyl group, a propyloxymethyl group, a propyloxyethyl group, a propyloxypropyl group, a propyloxybutyl group, a propyloxypentyl group, an i-propyloxymethyl group, an i-propyloxyethyl group, an i-propyloxypropyl group, an i-propyloxybutyl group, an i-propyloxypentyl group, a butyloxymethyl group, a butyloxyethyl group, a butyloxypropyl group, a butyloxybutyl group, an i-butyloxymethyl group, an i-butyloxyethyl group, an i-butyloxypropyl group, an i-butyloxybutyl group, a sec-butyloxymethyl group, a sec-butyloxyethyl group, a sec-butyloxypropyl group, a sec-butyloxybutyl group, a t-butyloxymethyl group, a t-butyloxyethyl group, a t-butyloxypropyl group, a t-butyloxybutyl group, a pentyloxymethyl group, a pentyloxyethyl group, a pentyloxypropyl group, a pentyloxybutyl group, a hexyloxymethyl group, a hexyloxyethyl group, a hexyloxypropyl group, etc.

[0043] The tri-lower alkylsilyl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded a trimethylsilyl group, a triethylsilyl group, a tripropylsilyl group or the like.

[0044] The lower alkylamino group is a linear or branched alkylamino group having up to 6 carbon atoms. This includes, for example, a methylamino group, an ethylamino group, an n-propylamino group, an i-propylamino group, an n-butylamino group, an i-butylamino group, a sec-butylamino group, a t-butylamino group, an n-pentylamino group, an i-pentylamino group, a sec-pentylamino group, a t-pentylamino group, a 2-methylbutylamino group, an n-hexylamino group, a 1-methylpentylamino group, a 2-methylpentylamino group, a 3-methylpentylamino group, a 4-methylpentylamino group, a 1-ethylbutylamino group, a 2-ethylbutylamino group, a 3-ethylbutylamino group, a 1,1-dimethylbutylamino group, a 2,2-dimethylbutylamino group, a 3,3-dimethylbutylamino group, a 1-ethyl-1-methylpropylamino group, etc. More preferred are a methylamino group, an ethylamino group, an n-propylamino group, an i-propylamino group, an n-butylamino group, an i-butylamino group, a sec-butylamino group, a t-butylamino group, etc.

[0045] The lower alkylthio group is a linear or branched alkylthio group having up to 6 carbon atoms. This includes, for example, a methylthio group, an ethylthio group, an n-propylthio group, an i-propylthio group, an n-butylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, an n-pentylthio group, an i-pentylthio group, a sec-pentylthio group, a t-pentylthio group, a 2-methylbutylthio group, an n-hexylthio group, an i-hexylthio group, a t-hexylthio group, a sec-hexylthio group, a 2-methylpentylthio group, a 3-methylpentylthio group, a 1-ethylbutylthio group, a 2-ethylbutylthio group, a 1,1-dimethylbutylthio group, a 2,2-dimethylbutylthio group, a 3,3-dimethylbutylthio group, a 1-ethyl-1-methylpropylthio group, etc. More preferred are a methylthio group, an ethylthio group, an n-propylthio group, an i-propylthio group, an n-butylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, etc.

[0046] The lower alkylthio-lower alkyl group is a linear or branched alkyl group having up to 6 carbon atoms, such as that mentioned hereinabove, as substituted with a linear or branched alkylthio group having up to 6 carbon atoms, such as that mentioned hereinabove.

[0047] The lower alkoxy carbonyl group is a linear or branched alkoxy carbonyl group with an alkyl moiety having up to 6 carbon atoms. This includes, for example, a methoxycarbonyl group, an ethoxycarbonyl group, an n-propyloxycarbonyl group, an i-propyloxycarbonyl group, an n-butyloxycarbonyl group, an i-butyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group, an n-pentyloxycarbonyl group, an i-pentyloxycarbonyl group, a sec-pentyloxycarbonyl group, a t-pentyloxycarbonyl group, a 2-methylbutyloxycarbonyl group, an n-hexyloxycarbonyl group, an i-hexyloxycarbonyl group, a t-hexyloxycarbonyl group, a sec-hexyloxycarbonyl group, a 2-methylpentyl oxycarbonyl group, a 3-methylpentyl oxycarbonyl group, a 1-ethylbutyloxycarbonyl group, a 2-ethylbutyloxycarbonyl group, a 1,1-dimethylbutyloxycarbonyl group, a 2,2-dimethylbutyloxycarbonyl group, a 3,3-dimethylbutyloxycarbonyl group, a 1-ethyl-1-methylpropyloxycarbonyl group, etc. More preferred are a methoxycarbonyl group, an ethoxycarbonyl group, an n-propyloxycarbonyl group, an i-propyloxycarbonyl group, an n-butyloxycarbonyl group, an i-butyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group.

[0048] The lower alkanoyl group is a linear or branched alkylcarbonyl group having up to 6 carbon atoms. This includes, for example, a methylcarbonyl group, an ethylcarbonyl group, an n-propylcarbonyl group, an i-propylcarbonyl group, an n-butylcarbonyl group, an i-butylcarbonyl group, a sec-butylcarbonyl group, a t-butylcarbonyl group, an n-pentylcarbonyl group, an i-pentylcarbonyl group, a sec-pentylcarbonyl group, a t-pentylcarbonyl group, a 2-methylbutylcarbonyl group, an n-hexylcarbonyl group, an i-hexylcarbonyl group, a t-hexylcarbonyl group, a sec-hexylcarbonyl group, a 2-methylpentylcarbonyl group, a 3-methylpentylcarbonyl group, a 1-ethylbutylcarbonyl group, a 2-ethylbutylcarbonyl group, a 1,1-dimethylbutylcarbonyl group, a 2,2-dimethylbutylcarbonyl group, a 3,3-dimethylbutylcarbonyl group, a 1-ethyl-1-methylpropylcarbonyl group, etc. More preferred are a methylcarbonyl group, an ethylcarbonyl group, an n-propylcarbonyl group, an i-propylcarbonyl group, an n-butyloxycarbonyl group, an i-butyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group, etc.

[0049] The lower alkanesulfonyl group is a linear or branched alkanesulfonyl group having up to 6 carbon atoms. This includes, for example, a methanesulfonyl group, an ethanesulfonyl group, a 1-propanesulfonyl group, a 2-propanesulfonyl group, a 1-butanesulfonyl group, a 2-butanesulfonyl group, a 1,1-dimethylethanesulfonyl group, a 1-(2-methylpropane)sulfonyl group, a 1-pentanesulfonyl group, a 2-pentanesulfonyl group, a 3-pentanesulfonyl group,

a 1-(3-methylbutane)sulfonyl group, a 1,1-dimethylpropanesulfonyl group, a 1-hexanesulfonyl group, a 2-hexanesulfonyl group, a 3-hexanesulfonyl group, a 1-(2-methylpentane)sulfonyl group, a 1-(3-methylpentane)sulfonyl group, a 1-(4-methylpentane)sulfonyl group, a 2-ethylbutanesulfonyl group, a 3-ethylbutanesulfonyl group, a 1,1-dimethylbutanesulfonyl group, a 2,2-dimethylbutanesulfonyl group, a 3,3-dimethylbutanensulfonyl group, a 1-ethyl-1-methylpropanesulfonyl group, etc.

[0050] The aryl group includes a phenyl group, and a naphthyl group. The terminology "naphthyl" as referred to herein includes 1-naphthyl and 2-naphthyl. The benzene ring or the naphthalene ring in this group may optionally be substituted by one or more substituents selected from a halogen atom, a lower alkyl group, a cyano group, a nitro group, a trifluoromethyl group and the like, such as those mentioned hereinabove.

[0051] The arylsulfonyl group is a sulfonyl group, to which is bonded an aryl group such as that mentioned hereinabove, and includes a benzenesulfonyl group, a toluenesulfonyl group, and a naphthalenesulfonyl group.

[0052] The aryl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded an aryl group such as that mentioned hereinabove, and includes, for example, a benzyl group, a 1-phenylethyl group, a 2-phenylethyl group, a phenylpropyl group, a phenylbutyl group, a phenylpentyl group, a phenylhexyl group, a naphthylmethyl group, a naphthylethyl group, a naphthylpropyl group, a naphthylbutyl group, a naphthylpentyl group, a naphthylhexyl group, etc.

[0053] The aryl-lower alkyloxy group includes, for example, a benzyloxy group, a 1-phenylethoxy group, a 2-phenylethoxy group, a phenylpropoxy group, a phenylbutyloxy group, a phenylpentyoxy group, a phenylhexyloxy group, a naphthylmethoxy group, a naphthylethoxy group, a naphthylpropoxy group, a naphthylbutyloxy group, a naphthylpentyoxy group, etc., in which the benzene ring or the naphthalene ring may optionally be substituted.

[0054] The arylsulfonyl-lower alkyl group is a lower alkyl group, such as that mentioned hereinabove, to which is bonded an arylsulfonyl group such as that mentioned hereinabove, and includes, for example, a benzenesulfonylmethyl group, a toluenesulfonylmethyl group, a naphthalenesulfonylmethyl group, etc.

[0055] The arylsulfonylamino group is an amino group to which is bonded an arylsulfonyl group such as that mentioned hereinabove, and this includes, for example, a benzenesulfonylamino group, a toluenesulfonylamino group, a naphthalenesulfonylamino group, etc.

[0056] The aryloxy group is an aryl group, such as that mentioned hereinabove, to which is bonded an oxygen atom, and this includes, for example, a phenoxy group, a 1-naphthoxy group, a 2-naphthoxy group, etc.

[0057] The arylcarbonyl group is a carbonyl group to which is bonded an aryl group such as that mentioned hereinabove, and this includes, for example, a phenylcarbonyl group, a naphthylcarbonyl group, etc.

[0058] The arylcarbonylamino group is an amino group to which is bonded an arylcarbonyl group such as that mentioned hereinabove, and this includes, for example, a phenylcarbonylamino group, a naphthylcarbonylamino group, etc.

[0059] The aryl-lower alkenyl group is an alkenyl group having 6 or less carbon atoms, which is substituted by an aryl group such as that mentioned hereinabove, and this includes, for example, a phenylethenyl group, a naphthylethenyl group, etc.

[0060] The heterocyclic group includes a pyridyl group, a quinolyl group, an isoquinolyl group, a thiazolyl group, a thiadiazolyl group, a benzofuranyl group, a dibenzofuranyl group, a thianaphthalenyl group, a 1H-1,2,3-triazolyl group, a 1,2,4-triazolyl group, a tetrazolyl group, a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a pyrimidinyl group, an indolyl group, and a benzimidazolyl group. The heterocyclic group may optionally be substituted by one or more substituents of halogen atoms and lower alkyl groups, such as those mentioned hereinabove, and the substituted heterocyclic group of that type includes, for example, a haloisoquinolyl group, a methylisoquinolyl group, etc.

[0061] The heterocyclic lower alkyl group means a lower alkyl group, such as that mentioned hereinabove, as substituted by a heterocyclic group, such as that mentioned hereinabove. This includes, for example, a pyridylmethyl group. The halo-heterocyclic lower alkyl group is a heterocyclic lower alkyl group, such as that mentioned hereinabove, in which the heterocyclic moiety is substituted with one or more halogens.

[0062] The heterocyclic lower alkylamino group is an amino group as substituted with a heterocyclic lower alkyl group, such as that mentioned hereinabove, and this includes, for example, a pyridylmethylamino group, etc. The heterocyclic lower alkylcarbamoyl group is a carbamoyl group as substituted with a heterocyclic lower alkyl group, such as that mentioned hereinabove, and this includes, for example, a pyridylmethylcarbamoyl group, etc.

[0063] The terminology "pyridyl" as referred to herein includes 2-pyridyl, 3-pyridyl and 4-pyridyl, for which the bonding position is not specifically defined. The same shall apply to the other heterocyclic groups as referred to herein, and that is, the bonding positions of the heterocyclic groups as referred to herein are not specifically defined.

[0064] The lower alkyleneedioxybenzyl group includes, for example, a methylenedioxybenzyl group, an ethylenedioxybenzyl group, a propylenedioxybenzyl group, etc.

[0065] A suitable heterocyclic group used herein means a saturated or unsaturated mono- or polycyclic hetero ring containing at least one hetero atom such as an oxygen atom, a sulfur atom, a nitrogen atom, etc.

[0066] Preferable examples thereof include the following heterocyclic groups:

- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolidinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g. tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, or the like;
- 5 • 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 3 sulfur atoms or S,S-dioxide thereof, such as dithianaphthalenyl (e.g. 4H-1,3-dithianaphthalenyl, 1,4-dithianaphthalenyl, etc.), benzothiophenyl or s,s-dioxide thereof (e.g. benzo[a]thiophenyl or S,S-dioxide thereof, benzo[b]thiophenyl or S,S-dioxide thereof, etc.), or the like;
- 10 • 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 4 nitrogen atoms, such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,3-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), dihydrotriazinyl (e.g. 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), or the like;
- 15 • 3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 4 nitrogen atoms, such as azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrazolidinyl, piperadiny, or the like;
- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as benzoazolyl, benzoazadiazolyl, or the like;
- 20 • 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl, isooxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), or the like;
- 25 • 3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as morpholinyl or the like;
- 7- to 12-membered, preferably 9- or 10-membered unsaturated condensed heterocyclic group (preferably bicyclic group) having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as benzothiazolyl, benzothiadiazolyl, or the like;
- 30 • 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl, 1,2-thiazolyl, thiadiazolyl (e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), or the like;
- 3- to 8-membered, preferably 5- or 6-membered saturated hetero monocyclic group having 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolidinyl;
- 3- to 8-membered, preferably 5- or 6-membered unsaturated hetero monocyclic group having one sulfur atom, such as thienyl or the like; etc.

[0067] Suitable "esterified carboxyl groups" are exemplified below.

[0068] The ester portion of the esterified carboxyl group suitably include a lower alkyl ester, such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tertiary butyl ester, pentyl ester, or hexyl ester, which may have at least one appropriate substituent. Examples of the lower alkyl ester include lower alkanoyloxy(lower)alkyl ester, such as acetoxyethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoxyloxy methyl ester, 1-(or 2-)acetoxyethyl ester, 1-(2-, or 3-)acetoxypropyl ester, 1-(2-, 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(2-, or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoxyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, or 1-(or 2-)pentanoyloxyethyl ester, lower alkanesulfonyl(lower)alkyl ester, such as 2-mesylethyl ester, mono(di, or tri)halo(lower)alkyl ester, such as 2-iodoethyl ester, 2,2,2-trichloroethyl ester, lower alkoxy carbonyloxy(lower)alkyl ester, such as methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, tertiary-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, or 1-(or 2-)isopropoxycarbonyloxyethyl ester, phthalizidene(lower)alkyl ester or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester, such as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, or (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, lower alkenyl ester, such as vinyl ester or allyl ester, lower alkynyl ester, such as ethynyl ester or propynyl ester, ar(lower)alkyl ester which may have at least one appropriate substituent, such as benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, or 4-hydroxy-3,5-di-tertiary-butylbenzyl ester, aryl ester which may have at least one appropriate substituent, such as phenyl ester, 4-chlorophenyl ester, tolyl ester, tertiary-butylphenyl ester, xylyl ester, mesityl ester, or cumenyl ester, phthalidyl ester, etc.

[0069] Preferable examples of a carboxyl group protected by esterification include lower alkoxy carbonyl and phenyl (or nitrophenyl)(C₁-C₄)alkoxy carbonyl. Most preferred are methoxycarbonyl, ethoxycarbonyl, and benzyloxycarbonyl.

[0070] Suitable amidated carboxyl groups include the following:

- a carbamoyl group;
- a mono- or di-lower alkyl carbamoyl group (as a lower alkyl group, those as described above can be used), such

as methylcarbamoyl, dimethylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, t-butylcarbamoyl, N-methyl-N-(pyridylmethyl)carbamoyl, or the like;

- an aryl(lower alkyl)carbamoyl (as an aryl group and a lower alkyl group, those as described above can be used), such as benzylcarbamoyl, 3,4-methylenedioxybenzylcarbamoyl, diaminobenzylcarbamoyl, or phenethylcarbamoyl;
- a cyclo(lower alkyl)carbamoyl having 3 to 7 carbon atoms (as a cyclo lower alkyl group, those as described above can be used), such as cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl or the like;
- an arylcarbamoyl group (as an aryl group, those as described above can be used), such as phenylcarbamoyl, naphthylcarbamoyl, or the like;
- a heterocyclic carbamoyl group (as a heterocyclic group, those as described above can be used), such as thiazolylcarbamoyl, thiadiazolylcarbamoyl, pyridylcarbamoyl, triazolylcarbamoyl, tetrazolylcarbamoyl, N-methyl-N-pyridinecarbamoyl, morpholinocarbamoyl, or the like;
- a heterocyclic(lower alkyl)carbamoyl group (as a heterocyclic lower alkyl group, those as described above can be used), such as morpholinoethylcarbamoyl, pyridylmethylcarbamoyl, methylenedioxybenzylcarbamoyl, or the like;
- an N-di-substituted carbamoyl group containing nitrogen as a member of a nitrogen-containing heterocyclic ring, such as morpholinocarbonyl, thiomorpholinocarbonyl, 1-perhydroazepinylcarbonyl, 1,1-dioxothiazolidinecarbonyl, piperidinocarbonyl, 1-piperazinylcarbonyl, 4-(2-hydroxyethyl)-1-piperazinylcarbonyl, 4-methyl-1-piperazinylcarbonyl, carboxypyrrolidinocarbonyl, or the like;
- a substituted sulfonylcarbamoyl group, etc.

[0071] The substituent for the substituted sulfonylcarbamoyl group includes the above-described groups such as the alkyl group having carbon atoms up to 8, the halo lower alkyl group, the aryl lower alkyl group, the hydroxy-lower alkyl group, the tri(lower alkyl)silyl(lower alkyl) group, the lower alkoxy-lower alkyl group, the lower alkylthio-lower alkyl group, the heterocyclic group, the aryl group, and the like. The aryl group may be substituted by a halogen atom, a lower alkyl group, a halo lower alkyl group, a lower alkoxy group, a nitro group, or the like. Specific examples of the substituted sulfonylcarbamoyl group include naphthylsulfonylcarbamoyl, benzenesulfonylcarbamoyl, nitrobenzenesulfonylcarbamoyl, trihalobenzenesulfonylcarbamoyl, lower alkoxybenzenesulfonylcarbamoyl, halobenzenesulfonylcarbamoyl, mono- or di-(lower alkyl) benzenesulfonylcarbamoyl, alkanesulfonylcarbamoyl having 1 to 8 carbon atoms, such as t-butylsulfonylcarbamoyl, butylsulfonylcarbamoyl, propylsulfonylcarbamoyl, isopropylsulfonylcarbamoyl, methylsulfonylcarbamoyl, octylsulfonylcarbamoyl, pentylsulfonylcarbamoyl, isopentylsulfonylcarbamoyl, hexylsulfonylcarbamoyl, or the like, trihalo(lower) alkylesulfonylcarbamoyl, phenyl(lower)alkylsulfonylcarbamoyl, tri-(lower)alkylsulfonylcarbamoyl, loweralkylthio(lower) alkylsulfonylcarbamoyl, lower alkoxy(lower)alkylsulfonylcarbamoyl, quinolinesulfonylcarbamoyl, or the like.

[0072] Suitable acyl groups include aliphatic acyl, aromatic acyl, heterocyclic acyl, and aliphatic acyl substituted with an aromatic group or a heterocyclic group, which are derived from carboxylic acid, carbonic acid, sulfonic acid, carbamic acid, and the like.

[0073] Examples of the aliphatic acyl include saturated or unsaturated non-cyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl such as lower alkyl sulfonyl (e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, iso-butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), alkoxy carbonyl such as lower alkoxy carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tertiary-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g. acryloyl, methacryloyl, chrotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclopantanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

[0074] Examples of the aromatic acyl include (C₆-C₁₀)aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), N-(C₆-C₁₀)arylcarbamoyl (e.g. N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.), (C₆-C₁₀) arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like.

[0075] Examples of the heterocyclic acyl include heterocyclic carbonyl, heterocyclic(lower)alkanoyl (e.g. heterocyclic acetyl, heterocyclic propanoyl, heterocyclic butanoyl, heterocyclic pentanoyl, heterocyclic hexanoyl, etc.), heterocyclic(lower)alkenoyl (e.g. heterocyclic propenoyl, heterocyclic butenoyl, heterocyclic pentenoyl, heterocyclic hexenoyl, etc.), heterocyclic glyoxyloyl, heterocyclic sulfinyl, heterocyclic sulfonyl, etc.

[0076] The aromatic group-bound aliphatic acyl includes aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.).

[0077] These acyl groups may be substituted with one or more appropriate substituents, such as a nitro group. An example thereof is nitroaralkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, etc.).

[0078] Preferred salts of the benzimidazole derivatives of the present invention are non-toxic, ordinary pharmaceut-

tically acceptable salts thereof. For example, mentioned are salts of the derivatives with bases as well as acid-addition salts of the derivatives, which include, for example, salts thereof with inorganic bases, such as salts with alkali metals (e.g., sodium, potassium); salts with alkaline earth metals (e.g., calcium, magnesium); ammonium salts; salts with organic amines (e.g., triethylamine, pyridine, picoline, ethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine); salts with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid); salts with organic carboxylic acids (e.g., formic acid, acetic acid, trifluoroacetic acid, maleic acid, tartaric acid); salts with sulfonic acids (e.g., methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid); salts with basic or acidic amino acids (e.g., arginine, aspartic acid, glutamic acid), etc.

[0079] The compounds of the invention could contain one or more chiral centers, therefore they could be enantiomers or diastereomers. A few of the compounds containing an alkenyl group could also be cis- or trans- isomers. In both cases, each of such isomers as well as the mixture thereof are within the scope of this invention.

[0080] The compounds of the invention can also exist as tautomers, and an individual of such tautomers and the mixture thereof are within the scope of this invention.

[0081] The compounds of the invention and their salts can be solvates, which are also within the scope of this invention. The solvent for the solvate is preferably water or ethanol.

[0082] Specific examples of benzimidazole derivatives of formula (IX) include 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole, 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)-benzimidazole, 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(2-propanesulfonylcarbamoyl)benzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole, 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole, N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acrylamide, N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide, 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)benzimidazole, 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole, 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(α -toluenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(4-nitrobenzenesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl)benzenesulfonylcarbamoyl]benzimidazole, 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole, 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole, 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole, 6-benzenesulfonylcarbamoyl-1-(4-benzyloxybenzyl)-2-methylbenzimidazole, 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]propionamide, 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)benzimidazole, 6-(4-t-butylbenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-ben-

zenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole, 5-benzenesulfonylcarbamoyl-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole, 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)benzimidazole, 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[(3-methylbutane)sulfonylcarbamoyl]-benzimidazole, 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole, 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl)propane]sulfonylcarbamoyl]-benzimidazole, 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-(1-ethanesulfonylcarbamoyl)-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 6-(1-ethanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 1-(2-chlorobenzyl)-6-[(2-methoxyethane)-sulfonylcarbamoyl]-2-methylbenzimidazole, 1-(2-chlorobenzyl)-2-methyl-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-2-methyl(1-pentanesulfonylcarbamoyl)-benzimidazole, 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]sulfonylcarbamoyl]-benzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]-benzimidazole, 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxy-ethanesulfonylcarbamoyl)benzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzyl)oxybenzyl]-benzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyl)oxybenzyl]-2-ethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)benzyl]-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxybenzyl)-benzimidazole, 6-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl)-benzimidazole, 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-phenylethyl)benzyl]-2-methylbenzimidazole, 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[4-(2-phenylethyl)benzyl]-benzimidazole, 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmethyl)benzimidazole, and 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]-benzimidazole, etc.

[0083] The benzimidazole derivatives and their pharmaceutically acceptable salts of the present invention that are mentioned hereinabove are effective for preventing and treating various disorders of, for example, impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), and hypertension based on their blood sugar level-depressing activity, as well as stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, and restenosis after PTCA based on their cGMP-PDB (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity, and antiallergic activity.

[0084] In addition, we, the present inventors, have further found that the benzimidazole derivatives which we have disclosed in Japanese Patent Application Laid-Open No. 5-222000 as c-GMP phosphodiesterase inhibitors also have the above-mentioned activities, and have now confirmed that these benzimidazole derivatives are also effective for preventing and treating the above-mentioned diseases and disorders like the compounds mentioned hereinabove.

[0085] The present invention further includes pharmaceutical compositions comprising, as an active ingredient, any of the above benzimidazole derivatives and their pharmaceutically acceptable salts, which are effective for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, etc.), syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cus-

ing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or 5 stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible 10 obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

[0086] To use the benzimidazole derivatives of the present invention for the manufacture of a medicament for treating diseases or disorders such as those mentioned hereinabove, they may be formulated into pharmaceutical compositions of ordinary forms, which comprise, as an active ingredient, any of the derivatives along with pharmaceutically acceptable carriers, such as organic or inorganic solid or liquid vehicles, and which are suitable for peroral administration, 15 parenteral administration or external application. The pharmaceutical compositions may be of any solid form of tablets, granules, powders, capsules, etc., or may be of any liquid form of solutions, suspensions, syrups, emulsions, lemonades, etc.

[0087] If desired, the pharmaceutical compositions may further contain a pharmaceutical aid, a stabilizer, a wetting agent, and also any ordinary additive of, for example, lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, 20 terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, etc.

[0088] The amount of the above-mentioned derivative of the present invention to be used shall vary, depending on the age and the condition of patients, the type and the condition of diseases or disorders, and the type of the derivative to be used. In general, for peroral administration, the dose of the derivative may be from 1 to 100 mg/kg; and for 25 intramuscular injection or intravenous injection, it may be from 0.1 to 10 mg/kg. Such a unit dose may be applied to a patient once to four times a day.

Fig. 1 shows chemical formulae of compound (42) to compound (47).

Fig. 2 shows chemical formulae of compound (48) to compound (53).

Fig. 3 shows chemical formulae of compound (54) to compound (59).

Fig. 4 shows chemical formulae of compound (60) to compound (65).

Fig. 5 shows chemical formulae of compound (66) to compound (71).

Fig. 6 shows chemical formulae of compound (72) to compound (77).

Fig. 7 shows chemical formulae of compound (78) to compound (83).

Fig. 8 shows chemical formulae of compound (84) to compound (89).

Fig. 9 shows chemical formulae of compound (90) to compound (95).

Fig. 10 shows chemical formulae of compound (96) to compound (101).

Fig. 11 shows chemical formulae of compound (102) to compound (107).

Fig. 12 shows chemical formulae of compound (108) to compound (113).

Fig. 13 shows chemical formulae of compound (114) to compound (119).

Fig. 14 shows chemical formulae of compound (120) to compound (125).

Fig. 15 shows chemical formulae of compound (126) to compound (131).

Fig. 16 shows chemical formulae of compound (132) to compound (137).

Fig. 17 shows chemical formulae of compound (138) to compound (143).

Fig. 18 shows chemical formulae of compound (144) to compound (149).

Fig. 19 shows chemical formulae of compound (150) to compound (155).

Fig. 20 shows chemical formulae of compound (156) to compound (161).

Fig. 21 shows chemical formulae of compound (162) to compound (167).

Fig. 22 shows chemical formulae of compound (168) to compound (173).

Fig. 23 shows chemical formulae of compound (174) to compound (179).

Fig. 24 shows chemical formulae of compound (180) to compound (185).

Fig. 25 shows chemical formulae of compound (186) to compound (191).

Fig. 26 shows chemical formulae of compound (192) to compound (197).

Fig. 27 shows chemical formulae of compound (198) to compound (203).

Fig. 28 shows chemical formulae of compound (204) to compound (209).

Fig. 29 shows chemical formulae of compound (210) to compound (215).

Fig. 30 shows chemical formulae of compound (216) to compound (221).

Fig. 31 shows chemical formulae of compound (222) to compound (227).

Fig. 32 shows chemical formulae of compound (228) to compound (233).

Fig. 33 shows chemical formulae of compound (234) to compound (239).
 Fig. 34 shows chemical formulae of compound (240) to compound (245).
 Fig. 35 shows chemical formulae of compound (246) to compound (251).
 Fig. 36 shows chemical formulae of compound (252) to compound (257).
 Fig. 37 shows chemical formulae of compound (258) to compound (263).
 Fig. 38 shows chemical formulae of compound (264) to compound (269).
 Fig. 39 shows chemical formulae of compound (270) to compound (275).
 Fig. 40 shows chemical formulae of compound (276) to compound (281).
 Fig. 41 shows chemical formulae of compound (282) to compound (287).
 Fig. 42 shows chemical formulae of compound (288) to compound (293).
 Fig. 43 shows chemical formulae of compound (294) to compound (299).
 Fig. 44 shows chemical formulae of compound (300) to compound (305).
 Fig. 45 shows chemical formulae of compound (306) to compound (311).
 Fig. 46 shows chemical formulae of compound (312) to compound (316).
 Fig. 47 shows chemical formulae of compound (317) to compound (322).
 Fig. 48 shows chemical formulae of compound (323) to compound (328).
 Fig. 49 shows chemical formulae of compound (329) to compound (334).
 Fig. 50 shows chemical formulae of compound (335) to compound (340).
 Fig. 51 shows chemical formulae of compound (341) to compound (346).
 Fig. 52 shows chemical formulae of compound (347) to compound (352).
 Fig. 53 shows chemical formulae of compound (353) to compound (358).
 Fig. 54 shows chemical formulae of compound (359) to compound (364).
 Fig. 55 shows chemical formulae of compound (365) to compound (370).
 Fig. 56 shows chemical formulae of compound (371) to compound (376).
 Fig. 57 shows chemical formulae of compound (377) to compound (382).
 Fig. 58 shows chemical formulae of compound (383) to compound (386).

[0089] The present invention is illustrated more specifically by referring to the following Examples. However, the present invention is not limited thereto.

Production Example 1

Production of ethyl 3-[N-(2-bromobenzyl)butyrylamino]-4-nitrobenzoate

[0090] One-hundred milligrams of sodium hydride (60% water-in-oil suspension) were added to a solution of 247 mg of ethyl 3-butyrylamino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide in a nitrogen atmosphere at room temperature in some divided portions. The reaction suspension was stirred at the same temperature for 1 hour, and a solution of 244 mg of 2-bromobenzyl bromide in 2 ml of N,N-dimethylformamide was gradually added dropwise thereto over a period of 10 minutes. The reaction mixture was stirred at room temperature for 1 hour, and was poured in ice water. The oily substance precipitated was extracted with methylene chloride. The organic solvent layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed through silica-gel flash column chromatography, and was eluted with a mixture of 25% ethyl acetate and n-hexane to give 540 mg of yellow oil of ethyl 3-[N-(2-bromobenzyl)butyrylamino]-4-nitrobenzoate.

[0091] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 0.87 (3H, t, J=8Hz), 1.48 (3H, t, J=8Hz), 1.68 (2H, sextet, J=8Hz), 2.03 (2H, t, J=8Hz), 4.30-4.46 (2H, m), 4.70 (1H, d, J=15Hz), 5.40 (1H, d, J=15Hz), 7.08-7.34 (2H, m), 7.43 (1H, dd, J=1, 8Hz), 7.58 (1H, dd, J=1, 8Hz), 7.66 (1H, d, J=1Hz), 7.96 (1H, d, J=8Hz), 8.16 (1H, dd, J=1, 8Hz)

Production Example 2

Production of ethyl 3-[N-(2-chlorobenzyl)benzoylamino]-4-nitrobenzoate

[0092] In the same manner as in Production Example 1, 480 mg of yellow crystals of ethyl 3-[N-(2-chlorobenzyl)benzoylamino]-4-nitrobenzoate were formed from 450 mg of ethyl 3-benzoylamino-4-nitrobenzoate and 243 mg of 2-chlorobenzyl bromide.

[0093] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 1.35 (3H, t, J=8Hz), 4.35 (2H, q, J=8Hz), 4.76 (1H, bd, J=15Hz), 5.82 (1H, bd, J=15Hz), 7.10-8.00 (12H, m)
mp : 111-113°C

5 Production Example 3

Production of ethyl 3-[N-(2-fluorobenzyl)butyrylamino]-4-nitrobenzoate

[0094] In the same manner as in Production Example 1, 394 mg of yellow oil of ethyl 3-[N-(2-fluorobenzyl)butyrylamino]-4-nitrobenzoate were formed from 300 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 243 mg of 2-fluorobenzyl bromide.

[0095] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 0.85 (3H, t, J=8Hz), 1.40 (3H, t, J=8Hz), 1.65 (2H, sextet, J=8Hz), 1.98 (2H, t, J=8Hz), 4.30-4.45 (2H, m), 4.60 (1H, d, J=10Hz), 5.25 (1H, d, J=10Hz), 6.88 (2H, t, J=8Hz), 7.08 (2H, dd, J=5, 8Hz), 7.24 (1H, dt, J=1, 8Hz), 7.41 (1H, dt, J=1, 8Hz), 7.69 (1H, d, J=1Hz), 7.96 (1H, d, J=8Hz), 8.15 (1H, dd, J=1, 8Hz)

Production Example 4

20 Production of ethyl 3-[N-(4-fluorobenzyl)butyrylamino]-4-nitrobenzoate

[0096] In the same manner as in Production Example 1, 400 mg of yellow oil of ethyl 3-[N-(4-fluorobenzyl)butyrylamino]-4-nitrobenzoate were formed from 300 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 243 mg of 4-fluorobenzyl bromide.

25 [0097] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 0.86 (3H, t, J=8Hz), 1.37 (3H, t, J=8Hz), 1.56-1.76 (2H, m), 1.96-2.04 (2H, m), 4.32-4.46 (2H, m), 4.40 (1H, d, J=14Hz), 5.23 (1H, d, J=14Hz), 6.95 (2H, t, J=8Hz), 7.10 (2H, dd, J=5, 8Hz), 7.47 (1H, d, J=1Hz), 7.95 (1H, d, J=8Hz), 8.16 (1H, dd, J=1, 8Hz)

30 Production Example 5

Production of ethyl 3-[N-(2-cyanobenzyl)butyrylamino]-4-nitrobenzoate

35 [0098] Potassium carbonate (296 mg) was added to a solution of 200 mg of ethyl 3-butyrylamino-4-nitrobenzoate and 154 mg of 2-cyanobenzyl bromide in N,N-dimethylformamide, and the mixture was stirred at 20 °C for 3 hours. The reaction mixture was extracted with ethyl acetate and with water. The organic layer was washed with water and with a sodium chloride aqueous solution, and was then dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give 330 mg of yellow oil of ethyl 3-[N-(2-cyanobenzyl)butyrylamino]-4-nitrobenzoate.

40 [0099] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 0.86 (3H, t, J=8Hz), 1.49 (3H, t, J=8Hz), 1.67 (2H, sextet, J=8Hz), 2.02 (2H, t, J=8Hz), 4.28-4.52 (2H, m), 4.90 (1H, d, J=15Hz), 5.28 (1H, d, J=15Hz), 7.40 (1H, t, J=8Hz), 7.61 (1H, dt, J=1, 8Hz), 7.70 (1H, d, J=1Hz), 7.74 (1H, dd, J=1, 8Hz), 8.02 (1H, d, J=10Hz), 8.22 (1H, dd, J=1, 10Hz)

45 Production Example 6

[0100] The following compounds were produced in the same manner as in Production Example 5.

50 Production Example 6-1

Ethyl 3-[N-(3-fluorobenzyl)butyrylamino]-4-nitrobenzoate

55 [0101] Properties of the compound:

yellow oil.

¹H-NMR (CDCl₃, δ) : 0.86 (3H, t, J=7.5Hz), 1.35 (3H, t, J=7.5Hz), 1.68 (2H, m), 2.00 (2H, t, J=7.5Hz), 4.36 (1H, d, J=15Hz), 4.40 (2H, m), 5.31 (1H, d, J=15Hz), 6.85-7.28 (4H, m), 7.60 (1H, d, J=1.5Hz), 7.97 (1H, d, J=10Hz),

8.16 (1H, dd, J=10,1.5Hz)

Production Example 6-2

5 Ethyl 4-nitro-3-[N-(2-pyridylmethyl)-n-butyrylamino] benzoate

[0102] This compound was used in the subsequent step at once.

[0103] Property of the compound:

10 yellow oil.

Production Example 6-3

Ethyl 3-[N-(2,6-dichlorobenzyl)butyrylamino]-4-nitrobenzoate

15 [0104] Properties of the compound:

1H-NMR (CDCl_3 , δ) : 0.89 (3H, t, J=7.5Hz), 1.38 (3H, t, J=7.5Hz), 1.70 (2H, m), 2.03 (2H, t, J=7.5Hz), 4.36 (2H, m), 4.96 (1H, d, J=13.5Hz), 5.70 (1H, d, J=13.5Hz), 7.10-7.28 (3H, m), 7.49 (1H, d, J=1.5Hz), 8.03 (1H, d, J=7.5Hz),
20 8.14 (1H, dd, J=7.5 and 1.5Hz)
mp : 85-89°C

Production Example 6-4

25 Ethyl 3-[N-(3-methylbenzyl)propionylamino]-4-nitrobenzoate

[0105] This compound was used in the subsequent step at once.

[0106] Property of the compound:

30 yellow oil.

Production Example 6-5

Ethyl 3-[N-(2-fluorobenzyl)cyclopropanecarbonylamino]-4-nitrobenzoate

35 [0107] Properties of the compound:

yellow oil.

1H-NMR (CDCl_3 , δ) : 0.60-0.71 (2H, m), 0.99-1.14 (3H, m), 1.38 (3H, t, J=7.5Hz), 4.37 (2H, m), 4.62 (1H, d, J=12Hz), 5.30 (1H, d, J=12Hz), 6.92 (1H, t, J=7.5Hz), 7.10 (1H, t, J=7.5Hz), 7.26 (1H, m), 7.42 (1H, t, J=7.5Hz),
40 7.80 (1H, s), 7.99 (1H, d, J=7.5Hz), 8.14 (1H, dd, J=7.5 and 2Hz)

Production Example 6-6

45 Ethyl 3-[N-(2-chlorobenzyl)cyclobutanecarbonylamino]-4-nitrobenzoate

[0108] Properties of the compound:

1H-NMR (CDCl_3 , δ) : 1.37 (3H, t, J=7.5Hz), 1.68-1.87 (4H, m), 2.22-2.58 (2H, m), 2.75-2.94 (1H, m), 4.23-4.46
50 (2H, m), 4.63 (1H, d, J=15Hz), 5.45 (1H, d, J=15Hz), 7.14-7.24 (3H, m), 7.35-7.45 (1H, m), 7.56 (1H, d, J=2Hz),
7.97 (1H, d, J=9Hz), 8.13 (1H, dd, J=9, 2Hz)

Production Example 6-7

55 Ethyl 3-cyclobutanecarbonylamino-4-nitrobenzoate

[0109] Properties of the compound:

1H-NMR (CDCl₃, δ) : 1.43 (3H, t, J=7.5Hz), 1.86-2.19 (2H, m), 2.22-2.54 (4H, m), 3.20-3.41 (1H, m), 4.43 (2H, q, J=7.5Hz), 7.80 (1H, dd, J=10, 2Hz), 8.26 (1H, d, J=10Hz), 9.45 (1H, d, J=2Hz)
mp : 94-96°C

5 Production Example 7

Production of 3-acetylamino-4-nitrobenzamide

[0110] Oxaly chloride (3.91 ml) was added dropwise to a solution of 7.00 g of 3-acetylamino-4-nitrobenzoic acid in 50 ml of dichloromethane in a nitrogen atmosphere while being cooled with ice, and the mixture was stirred for 1 hour while being cooled with ice and then at room temperature for 2.5 hours. The reaction solvent was distilled off under reduced pressure, and the residue was then dissolved in 50 ml of tetrahydrofuran. The solution was added dropwise to 28% aqueous ammonia in a nitrogen atmosphere while being cooled with ice. The reaction solution was stirred for 1 hour, and water and ethyl acetate were added thereto. Approximately 8 g of the solid material precipitated were collected through filtration. After the filtrate was separated, the organic layer was washed with water, and dried over magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain the residue. The solid material precipitated and the residue were combined, washed with hot ethyl acetate, and collected through filtration to give 4.94 g of 3-acetylamino-4-nitrobenzamide.

[0111] Properties of the compound:

1H-NMR (DMSO-d6, δ) : 2.08 (3H, s), 7.68 (1H, br s), 7.78 (1H, dd, J=9, 2Hz), 7.94-8.05 (2H, m), 8.23 (1H, brs)
Mass (FAB) : 224

25 Production Example 8

Production of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide

[0112] 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide was produced from the compound in the same manner as in Production Example 7.

[0113] Properties of the compound:

1H-NMR (DMSO-d6, δ) : 1.86 (3H, s), 4.64 (1H, d, J=15Hz), 5.06 (1H, d, J=15Hz), 7.22-7.40 (4H, m), 7.73 (1H, br s), 7.84 (1H, d, J=2Hz), 8.03 (1H, dd, J=9, 2Hz), 8.14 (1H, d, J=9Hz), 8.22 (1H, br s)

35 Production Example 9

Production of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenznitrile

[0114] Thirty milliliters of 1,4-dioxane were added dropwise to a solution of 1.70 ml of titanium tetrachloride in 4 ml of dichloromethane in a nitrogen atmosphere while being cooled with ice. Then, a solution of 2.70 g of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzamide in 65 ml of 1,4-dioxane was added dropwise thereto. After the mixture was stirred for 15 minutes, 3.14 g of triethylamine were added thereto, and the mixture was stirred for 2 hours while being cooled with ice. After the completion of the reaction, the solvent was distilled off under reduced pressure, and the residue was extracted with ethyl acetate and with water. The organic layer was washed with water, and was dried over magnesium sulfate. Subsequently, the solvent was distilled off under reduced pressure. The residue was purified through column chromatography [200 ml, a mixture of n-hexane and ethyl acetate at a ratio of 4:1] to give 1.21 g of 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenznitrile.

[0115] Properties of the compound:

1H-NMR (CDCl₃, δ) : 1.92 (3H, s), 4.61 (1H, d, J=15Hz), 5.40 (1H, d, J=15Hz), 7.18-7.50 (5H, m), 7.80 (1H, dd, J=9, 2Hz), 8.01 (1H, d, J=9Hz)
Mass (FAB) : 300
IR (Nujol) : 2250cm⁻¹

55 Production Example 10

Production of 3-[N-(2-chlorobenzyl)amino]-4-nitrobenznitrile

[0116] One milliliter of 35% hydrochloric acid was added to a solution of 850 mg of 3-[N-(2-chlorobenzyl)acetylamino]-

4-nitrobenzamide in 10 ml of 1,4-dioxane, and the mixture was heat-refluxed for 4 days. After the solvent was distilled off from the reaction solution under reduced pressure, the residue was separated by being poured in a mixture solution of water and chloroform. The organic layer was washed with water, and was dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified through column chromatography [50 ml, chloroform] to give 230 mg of 3-[N-(2-chlorobenzyl)amino]-4-nitrobenzonitrile.

[0117] Properties of the compound:

¹H-NMR (CDCl₃, δ) : 4.65 (2H, d, J=6Hz), 6.93 (1H, dd, J=9, 2Hz), 7.10 (1H, d, J=2Hz), 7.25-7.40 (3H, m), 7.40-7.54 (1H, m), 8.30 (1H, d, J=9Hz), 8.45 (1H, br s)

Mass (FAB) : 258

IR (Nujol) : 2220cm⁻¹

Production Example 11

Production of 4-amino-3-[N-(2-chlorobenzyl)amino]-benzonitrile

[0118] Fifty milligrams of 10% palladium on carbon were added to a mixed solution of 261 mg of 3-[N-(2-chlorobenzyl)amino]-4-nitrobenzonitrile, 15 ml of methanol and 3 ml of 1,4-dioxane to conduct the catalytic reduction in a hydrogen atmosphere at 3 atm. After the completion of the reaction, the reaction solution was filtered through celite, and the filtrate was distilled off under reduced pressure. The resulting solid material was washed with ether, and was collected through filtration to give 196 mg of 4-amino-3-[N-(2-chlorobenzyl)amino]benzonitrile.

[0119] Properties of the compound:

¹H-NMR (DMSO-d6, δ) : 4.39 (2H, d, J=5Hz), 5.57 (1H, t, J=5Hz), 5.69 (2H, s), 6.46 (1H, d, J=2Hz), 6.61 (1H, d, J=9Hz), 6.88 (1H, dd, J=9, 2Hz), 7.25-7.41 (3H, m), 7.44-7.54 (1H, m)

Example 1 (Reference example)

Synthesis of 1-(2-bromobenzyl)-6-ethoxycarbonyl-2-n-propyl-benzimidazole (42)

[0120] A suspension obtained by adding 390 mg of ethyl 3-[N-(2-bromobenzyl)butyrylamino]-4-nitrobenzoate and 210 mg of reduced iron to a mixed solution of 1 ml of acetic acid and 2 ml of ethanol was refluxed for 1 hour while being vigorously stirred. After the completion of the reaction, the reaction solution was cooled down and filtered through celite, and the filtrate was then concentrated under reduced pressure. The residue was separated with the addition of ethyl acetate and a sodium hydrogencarbonate aqueous solution. After the organic solvent layer was dried, the solvent was distilled off under reduced pressure, and the brown residue was obtained. This residue was purified through flash column chromatography to give 160 mg of yellow crystals of 1-(2-bromobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (42).

[0121] Properties of Compound (42):

¹H-NMR (CDCl₃, δ) : 1.04 (3H, t, J=8Hz), 1.40 (3H, t, J=8Hz), 1.78-1.98 (2H, m), 2.34 (2H, t, J=8Hz), 4.38 (2H, q, J=8Hz), 5.45 (2H, s), 6.65 (1H, t, J=8Hz), 7.00 (1H, t, J=8Hz), 7.13 (1H, t, J=8Hz), 7.28 (1H, t, J=8Hz), 7.78 (1H, d, J=10Hz), 7.99 (1H, d, J=10Hz), 8.02 (1H, s)
mp : 134-135°C

Example 2 (Reference example)

Synthesis of 1-(2-cyanobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (43)

[0122] In the same manner as in Example 1, 160 mg of colorless crystals of 1-(2-cyanobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (43) were formed from 390 mg of ethyl 3-[N-(2-cyanobenzyl)butyrylamino]-4-nitrobenzoate.

[0123] Properties of Compound (43):

¹H-NMR (CDCl₃, δ) : 1.04 (3H, t, J=8Hz), 1.40 (3H, t, J=8Hz), 1.88 (2H, sextet, J=8Hz), 2.80 (2H, t, J=8Hz), 4.38 (2H, q, J=8Hz), 5.62 (2H, s), 6.57-6.63 (1H, m), 7.38-7.50 (2H, m), 7.78 (1H, dd, J=1, 8Hz), 7.79 (1H, d, J=8Hz), 7.94 (1H, d, J=1Hz), 8.03 (1H, dd, J=1, 8Hz)
mp : 132-134°C

Example 3 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-phenyl-benzimidazole (44)

5 [0124] In the same manner as in Example 1, 220 mg of yellow crystals of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-phenyl-benzimidazole (44) were obtained from 460 mg of ethyl 3-[N-(2-chlorobenzyl)benzoylamino]-4-nitrobenzoate.

[0125] Properties of Compound (44):

10 $^1\text{H-NMR}$ (CDCl_3 , δ) : 1.40 (3H, t, $J=8\text{Hz}$), 4.38 (2H, q, $J=8\text{Hz}$), 5.56 (2H, s), 6.72 (1H, dd, $J=1, 8\text{Hz}$), 7.18 (1H, dt, $J=1, 8\text{Hz}$), 7.30 (1H, dt, $J=1, 8\text{Hz}$), 7.45-7.55 (4H, m), 7.64 (1H, d, $J=1\text{Hz}$), 7.68 (1H, d, $J=1\text{Hz}$), 7.90 (1H, d, $J=10\text{Hz}$), 7.95 (1H, s), 8.08 (1H, dd, $J=1, 8\text{Hz}$)
mp : 140-142°C

Example 4 (Reference example)

15 Synthesis of 6-ethoxycarbonyl-1-(2-fluorobenzyl)-2-n-propylbenzimidazole (45)

[0126] In the same manner as in Example 1, 160 mg of colorless crystals of 6-ethoxycarbonyl-1-(2-fluorobenzyl)-2-n-propylbenzimidazole (45) were formed from 390 mg of ethyl 3-[N-(2-fluorobenzyl)butyrylamino]-4-nitrobenzoate.

20 [0127] Properties of Compound (45):

1H-NMR (CDCl_3 , δ) : 1.04 (3H, t, $J=8\text{Hz}$), 1.40 (3H, t, $J=8\text{Hz}$), 1.78-1.98 (2H, m), 2.34 (2H, t, $J=8\text{Hz}$), 4.38 (2H, q, $J=8\text{Hz}$), 5.45 (2H, s), 6.65 (1H, t, $J=8\text{Hz}$), 7.00 (1H, t, $J=8\text{Hz}$), 7.13 (1H, t, $J=8\text{Hz}$), 7.28 (1H, t, $J=8\text{Hz}$), 7.78 (1H, d, $J=10\text{Hz}$), 7.99 (1H, d, $J=10\text{Hz}$), 8.02 (1H, s)
mp : 134-135°C

Example 5 (Reference example)

Synthesis of 6-ethoxycarbonyl-1-(4-fluorobenzyl)-2-n-propylbenzimidazole (46)

30 [0128] In the same manner as in Example 1, 160 mg of colorless crystals of 6-ethoxycarbonyl-1-(4-fluorobenzyl)-2-n-propylbenzimidazole (46) were formed from 400 mg of ethyl 3-[N-(4-fluorobenzyl)butyryl]amino]-4-nitrobenzoate.

[0129] Properties of Compound (46):

35 $^1\text{H-NMR}$ (CDCl_3 , δ) : 1.04 (3H, t, $J=8\text{Hz}$), 1.40 (3H, t, $J=8\text{Hz}$), 1.88 (2H, sextet, $J=8\text{Hz}$), 2.82 (2H, t, $J=8\text{Hz}$), 4.38 (2H, q, $J=8\text{Hz}$), 5.38 (2H, s), 7.00 (4H, d, $J=7\text{Hz}$), 7.77 (1H, d, $J=8\text{Hz}$), 7.98 (1H, d, $J=1\text{Hz}$), 8.00 (1H, dd, $J=1, 8\text{Hz}$)
mp : 134-135°C

Example 6 (Reference example)

40 [0130] The following compounds were formed in the same manner as in Example 1.

Example 6-1 (Reference example)

45 6-Ethoxycarbonyl-2-n-propyl-1-(2-pyridylmethyl)benzimidazole (47)

[0131] Properties of Compound (47):

50 $^1\text{H-NMR}$ (CDCl_3 , δ) : 1.03 (3H, t, $J=7.5\text{Hz}$), 1.39 (3H, t, $J=7.5\text{Hz}$), 1.89 (2H, m), 2.86 (2H, t, $J=7.5\text{Hz}$), 4.38 (2H, q, $J=7.5\text{Hz}$), 5.50 (2H, s), 6.72 (1H, d, $J=7.5\text{Hz}$), 7.24 (1H, m), 7.58 (1H, dt, $J=7.5, 1.5\text{Hz}$), 7.79 (1H, d, $J=7.5\text{Hz}$), 7.96-8.02 (2H, m), 8.60 (1H, d, $J=4\text{Hz}$)
mp : 84-85°C

Example 6-2 (Reference example)

55 6-Ethoxycarbonyl-1-(3-fluorobenzyl)-2-n-propylbenzimidazole (48)

[0132] Properties of Compound (48):

EP 0 882 718 B1

1H-NMR (CDCl₃, δ) : 1.04 (3H, t, J=7.5Hz), 1.39 (3H, t, J=7.5Hz), 1.90 (2H, m), 2.81 (2H, t, J=7.5Hz), 4.39 (2H, q, J=7.5Hz), 5.39 (2H, s), 6.70-6.84 (2H, m), 7.00 (1H, dt, J=8.5 and 1.5Hz), 7.78 (1H, d, J=8.5Hz), 7.96 (1H, s), 8.00 (1H, d, J=8.5Hz)
mp : 142-146°C

5

Example 6-3 (Reference example)

1-(2,6-Dichlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (49)

10 [0133] Properties of Compound (49) :

1H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=7.5Hz), 1.38 (3H, t, J=7.5Hz), 1.88 (2H, m), 2.93 (2H, t, J=7.5Hz), 4.34 (2H, q, J=7.5Hz), 5.61 (2H, s), 7.26 (1H, d, J=7.5Hz), 7.39 (2H, d, J=7.5Hz), 7.68 (1H, d, J=7.5Hz), 7.84 (1H, d, J=1.5Hz), 7.91 (2H, d, J=7.5Hz)
mp : 153-156°C

15

Example 6-4 (Reference example)

1-(3-Methylbenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (50)

20

[0134] Properties of Compound (50):

colorless solid.

1H-NMR (CDCl₃, δ) : 1.02 (3H, t, J=7.5Hz), 1.41 (3H, t, J=7.5Hz), 1.89 (2H, m), 2.29 (3H, s), 2.82 (2H, t, J=7.5Hz), 4.38 (2H, q, J=7.5Hz), 5.35 (2H, s), 6.79-6.86 (2H, m), 7.09 (1H, d, J=7.5Hz), 7.20 (1H, t, J=7.5Hz), 7.76 (1H, d, J=7.5Hz), 7.95-8.02 (2H, m)

Example 6-5 (Reference example)

30 2-Cyclopropyl-6-ethoxycarbonyl-1-(2-fluorobenzyl)benzimidazole (51)

[0135] Properties of Compound (51):

1H-NMR (CDCl₃, δ) : 1.10 (2H, m), 1.27 (2H, m), 1.40 (3H, t, J=7.5Hz), 1.95 (1H, m), 4.37 (2H, q, J=7.5Hz), 5.56 (2H, s), 6.77 (1H, t, J=7.5Hz), 7.03 (1H, t, J=7.5Hz), 7.13 (1H, t, J=7.5Hz), 7.29 (1H, m), 7.69 (1H, d, J=7.5Hz), 7.96 (1H, d, J=7.5Hz), 8.02 (1H, d, J=2Hz)
mp : 122-126°C

35

Example 6-6 (Reference example)

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1-(2-Chlorobenzyl)-6-cyano-2-cyclopropylbenzimidazole (52)

[0136] Properties of Compound (52):

1H-NMR (CDCl₃, δ) : 1.04-1.24 (2H, m), 1.24-1.39 (2H, m), 1.83-2.01 (1H, m), 5.58 (2H, s), 6.54 (1H, d, J=9Hz), 7.16 (1H, td, J=9, 2Hz), 7.22-7.38 (1H, m), 7.43-7.56 (3H, m), 7.74 (1H, dd, J=9, 2Hz)
Mass (FAB) : 308 (M+1)
IR (Nujol) : 2210cm⁻¹

45

Example 6-7 (Reference example)

1-(2-Chlorobenzyl)-2-cyclobutyl-6-ethoxycarbonylbenzimidazole (53)

[0137] Properties of Compound (53):

50

1H-NMR (CDCl₃, δ) : 1.38 (3H, t, J=7.5Hz), 1.90-2.21 (2H, m), 2.21-2.24 (2H, m), 2.46-2.70 (2H, m), 3.52-3.73 (1H, m), 4.37 (2H, q, J=7.5Hz), 5.39 (2H, s), 6.34 (1H, dd, J=9, 2Hz), 7.06 (1H, td, J=9, 2Hz), 7.23 (1H, td, J=9, 2Hz), 7.46 (1H, dd, J=9, 2Hz), 7.83 (1H, d, J=9Hz), 7.92 (1H, d, J=2Hz), 8.01 (1H, dd, J=9, 2Hz)

mp : 111-113°C

Example 6-8 (Reference example)

5 1-(2-Chlorobenzyl)-6-ethoxycarbonyl-2-n-pentylbenzimidazole (54)

[0138] Properties of Compound (54):

10 ¹H-NMR (CDCl₃, δ) : 0.87 (3H, t, J=7.5Hz), 1.22-1.47 (7H, m), 1.74-1.93 (2H, m), 2.80 (2H, t, J=7.5Hz), 4.37 (2H, q, J=7.5Hz), 5.47 (2H, s), 6.39 (1H, dd, J=9, 2Hz), 7.08 (1H, td, J=9, 2Hz), 7.19-7.33 (1H, m), 7.48 (1H, dd, J=9, 2Hz), 7.79 (1H, d, J=9Hz), 7.94 (1H, d, J=2Hz), 8.00 (1H, dd, J=9, 2Hz)

Example 7 (Reference example)

15 5-Carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (55)

20 [0139] Twenty milliliters of ethanol and 10.4 g of a 10% sodium hydroxide aqueous solution were added to 2.8 g of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-n-propylbenzimidazole, and the mixture was heat-refluxed for 4 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The crystals were collected, washed with water, and dried under reduced pressure to give 2.46 g of a colorless solid of 5-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (55).

[0140] Properties of Compound (55):

25 ¹H-NMR (DMSO-d6, δ) : 0.93 (3H, t, J=7.5Hz), 1.75 (2H, m), 2.79 (2H, t, J=7.5Hz), 5.61 (2H, s), 6.49 (1H, d, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.33 (1H, t, J=7.5Hz), 7.46 (1H, d, J=7.5Hz), 7.56 (1H, d, J=7.5Hz), 7.80 (1H, d, J=7.5Hz), 8.20 (1H, s)

Example 8 (Reference example)

30 [0141] The following compounds were formed in the same manner as in Example 7.

Example 8-1 (Reference example)

35 6-Carboxy-1-(3-methylbenzyl)-2-n-propylbenzimidazole (56)

[0142] Properties of Compound (56):

colorless solid.

40 ¹H-NMR (DMSO-d6, δ) : 0.97 (3H, t, J=7.5Hz), 1.78 (2H, m), 2.23 (3H, s), 3.86 (2H, q, J=7.5Hz), 5.53 (2H, s), 6.80 (1H, d, J=7.5Hz), 6.91 (1H, s), 7.07 (1H, d, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.65 (1H, d, J=7.5Hz), 7.79 (1H, d, J=7.5Hz), 8.04 (1H, s)

Example 8-2 (Reference example)

45 2-n-Butyl-7-carboxy-1-(2-chlorobenzyl)benzimidazole (57)

[0143] Properties of Compound (57):

50 ¹H-NMR (DMSO-d6, δ) : 0.84 (3H, t, J=7.5Hz), 1.34 (2H, m), 1.71 (2H, m), 2.80 (2H, t, J=7.5Hz), 5.89 (2H, s), 6.03 (1H, d, J=7.5Hz), 7.13 (1H, t, J=7.5Hz), 7.27 (2H, t, J=7.5Hz), 7.48 (1H, d, J=7.5Hz), 7.63 (1H, d, J=7.5Hz), 7.87 (1H, d, J=7.5Hz)

Example 8-3 (Reference example)

55 6-Carboxy-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (58)

[0144] Properties of Compound (58):

¹H-NMR (DMSO-d₆, δ) : 1.04-1.19 (4H, m), 2.37 (1H, m), 5.79 (2H, s), 7.00 (1H, t, J=7.5Hz), 7.15 (1H, t, J=7.5Hz), 7.27 (1H, t, J=10.5Hz), 7.37 (1H, m), 7.60 (1H, d, J=7.5Hz), 7.82 (1H, d, J=7.5Hz), 8.11 (1H, s)
mp : 224-229°C

5 Example 8-4 (Reference example)

2-n-Butyl-6-carboxy-1-(2-fluorobenzyl)benzimidazole (59)

10 [0145] Properties of Compound (59):

¹H-NMR (DMSO-d₆, δ) : 0.87 (3H, t, J=7.5Hz), 1.26-1.48 (2H, m), 1.60-1.80 (2H, m), 2.90 (2H, t, J=7.5Hz), 5.63 (2H, s), 6.89 (1H, td, J=9, 2Hz), 7.13 (1H, td, J=9, 2Hz), 7.20-7.44 (2H, m), 7.64 (1H, d, J=9Hz), 7.80 (1H, dd, J=9, 2Hz), 8.08 (1H, d, J=2Hz)
mp : 216-219°C

15 Example 9 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (60)

20 [0146] Oxalyl chloride (0.208 ml) was added dropwise to a suspension prepared by adding 390 mg of 6-carboxy-1-(2-chlorobenzyl)-2-cyclopropylbenzimidazole to 10 ml of methylene chloride containing 1 drop of N,N-dimethylformamide at room temperature over a period of several minutes. The mixture was stirred at the same temperature for 2 hours, and was then concentrated under reduced pressure. Isopropyl ether was added to the residue, and the mixture was pulverized to give 450 mg of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (60) as a white powder. Since this product was unstable, it was used as a starting material in the subsequent step without being purified.

25 Example 10 (Reference example)

30 Synthesis of 1-(2-chlorobenzyl)-6-(4-dimethylaminophenylmethylcarbamoyl)-2-n-propylbenzimidazole (61)

35 [0147] Four-hundred milligrams of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were dissolved in 3 ml of methylene chloride containing 1 drop of N,N-dimethylformamide. Oxalyl chloride (28 mg) was added to this solution at 5°C. The thus-obtained solution was stirred at room temperature for 1 hour, and was then concentrated under reduced pressure. The residue was dissolved in 3 ml of methylene chloride, and the mixture was added to a mixed solution prepared by adding 271 mg of 4-dimethylaminobenzylamine hydrochloride and 1 ml of triethylamine to 10 ml of methylene chloride at room temperature. The resulting reaction mixture was stirred at the same temperature for 1 hour, washed with water, dried and then concentrated under reduced pressure. The residue was developed and purified through thin-layer chromatography to give 215 mg of 1-(2-chlorobenzyl)-6-(4-dimethylaminophenylmethylcarbamoyl)-2-n-propylbenzimidazole (61).

40 [0148] Properties of Compound (61):

colorless crystals.

¹H-NMR (CDCl₃, δ) : 1.01 (3H, t, J=7Hz), 1.88 (2H, sextet, J=7Hz), 2.76 (2H, t, J=7Hz), 2.95 (6H, s), 4.50 (2H, d, J=5Hz), 5.45 (2H, s), 6.32 (1H, d, J=5Hz), 6.36 (1H, d, J=7Hz), 6.72 (2H, d, J=10Hz), 7.07 (1H, dt, J=1, 8Hz), 7.20-7.25 (3H, m), 7.46 (1H, dd, J=1, 8Hz), 7.58 (1H, dd, J=1, 8Hz), 7.76 (1H, d, J=8Hz), 7.82 (1H, d, J=1Hz)
mp : 155-156°C

50 Example 11 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-6-morpholino-carbamoyl-2-n-propylbenzimidazole (62)

55 [0149] In the same manner as in Example 10, 205 mg of 1-(2-chlorobenzyl)-6-morpholinocarbamoyl-2-n-propylbenzimidazole (62) were formed from 200 mg of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole and 124 mg of 4-aminomorpholine.

[0150] Properties of Compound (62):

colorless crystals.

⁵ ¹H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=8Hz), 1.88 (2H, sextet, J=8Hz), 2.62 (4H, bs), 2.72 (2H, t, J=8Hz), 3.85 (4H, bs), 5.42 (2H, s), 6.42 (1H, dd, J=1, 8Hz), 7.08 (1H, dt, J=1, 8Hz), 7.20-7.28 (3H, m), 7.47 (1H, dd, J=1, 8Hz), 7.78 (1H, dd, J=1, 8Hz)
mp : 195-197°C

Example 12 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-n-propyl-6-thiomorpholinocarbonylbenzimidazole (63)

¹⁰ [0151] In the same manner as in Example 10, 160 mg of 1-(2-chlorobenzyl)-2-n-propyl-6-thiomorpholinocarbonylbenzimidazole (63) were formed from 200 mg of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole and 125 mg of thiomorpholine.

[0152] Properties of Compound (63):

¹⁵ colorless crystals.
¹H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=8Hz), 1.88 (2H, sextet, J=8Hz), 2.78 (2H, t, J=8Hz), 2.96 (4H, bt, J=5Hz), 3.88 (4H, bt, J=5Hz), 5.46 (2H, s), 6.34 (1H, dd, J=1, 8Hz), 7.08 (1H, dt, J=1, 8Hz), 7.26 (2H, dt, J=1, 8Hz), 7.47 (1H, dd, J=1, 8Hz), 7.58 (1H, bd, J=8Hz), 7.76 (1H, s), 7.78 (1H, d, J=8Hz)
mp : 160-162°C

Example 13 (Reference example)

Synthesis of 2-n-butyl-1-(2-chlorobenzyl)-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (64)

²⁵ [0153] In the same manner as in Example 10, 230 mg of 2-n-butyl-1-(2-chlorobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (64) were formed from 200 mg of 6-carboxy-2-n-butyl-1-(2-chlorobenzyl)-benzimidazole and 126 mg of 2-aminomethylpyridine.

[0154] Properties of Compound (64):

³⁰ colorless crystals.
¹H-NMR (CDCl₃, δ) : 0.92 (3H, t, J=8Hz), 1.42 (2H, sextet, J=8Hz), 1.82 (2H, quintet, J=8Hz), 2.82 (2H, t, J=8Hz), 4.76 (1H, d, J=5Hz), 5.46 (2H, s), 6.38 (1H, dd, J=1, 8Hz), 7.08 (1H, dt, J=1, 8Hz), 7.18-7.26 (2H, m), 7.32 (1H, d, J=8Hz), 7.46 (1H, dd, J=1, 8Hz), 7.62 (1H, dt, J=1, 8Hz), 7.72 (1H, dt, J=1, 8Hz), 7.82 (1H, d, J=8Hz), 7.88 (1H, d, J=1Hz), 8.56 (1H, dd, J=1, 8Hz)
mp : 175-176°C

Example 14 (Reference example)

Synthesis of 2-n-butyl-5-carbamoyl-1-(2-chlorobenzyl) benzimidazole (65)

⁴⁰ [0155] In the same manner as in Example 10, 170 mg of 2-n-butyl-5-carbamoyl-1-(2-chlorobenzyl)benzimidazole (65) were formed from 100 mg of 2-n-butyl-1-(2-chlorobenzyl)-5-carboxybenzimidazole.

[0156] Properties of Compound (65):

⁴⁵ colorless crystals.
¹H-NMR (DMSO-d₆, δ) : 0.84 (3H, t, J=8Hz), 1.35 (2H, sextet, J=8Hz), 1.68 (2H, quintet, J=8Hz), 2.78 (2H, t, J=8Hz), 5.58 (2H, s), 6.50 (1H, dd, J=1, 8Hz), 7.25 (1H, dt, J=1, 8Hz), 7.28 (1H, bs), 7.35 (1H, dt, J=1, 8Hz), 7.42 (1H, d, J=10Hz), 7.56 (1H, dd, J=1, 8Hz), 7.74 (1H, dd, J=1, 10Hz), 7.96 (1H, bs), 8.20 (1H, d, J=1Hz)
mp : 195-198°C

Example 15 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-cyclopropyl-6-morpholinocarbonylbenzimidazole (66)

⁵⁵ [0157] 1-(2-Chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride (140 mg) was added to a solution prepared by adding 298 mg of morpholine (30% methanol solution) to 10 ml of methylene chloride at room temperature. The reaction mixture was stirred at the same temperature for 1 hour, then washed with water, dried, and concentrated under reduced pressure. The residue was recrystallized with ether to give 20 mg of 1-(2-chlorobenzyl)-

2-cyclopropyl-6-morpholinocarbonylbenzimidazole. (66).

[0158] Properties of Compound (66):

colorless crystals.

⁵ ¹H-NMR (CDCl₃, δ) : 1.04-1.12 (2H, m), 1.25-1.32 (2H, m), 1.82-1.96 (1H, m), 3.68 (8H, bs), 5.56 (2H, s), 6.55 (1H, dd, J=1, 8Hz), 7.13 (1H, dt, J=1, 8Hz), 7.22-7.29 (2H, m), 7.30 (1H, d, J=1Hz), 7.46 (1H, dd, J=1, 8Hz), 7.77 (1H, d, J=8Hz)
mp : 193-195°C

¹⁰ Example 16 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-cyclopropyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (67)

[0159] In the same manner as in Example 15, 95 mg of 1-(2-chlorobenzyl)-2-cyclopropyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (67) were formed from 150 mg of 1-(2-chlorobenzyl)-6-chlorocarbonyl-2-cyclopropylbenzimidazole hydrochloride and 85 mg of 2-aminomethylpyridine.

[0160] Properties of Compound (67):

colorless crystals.

²⁰ ¹H-NMR (CDCl₃, δ) : 1.02-1.13 (2H, m), 1.24-1.32 (2H, m), 1.82-1.95 (1H, m), 4.76 (2H, d, J=5Hz), 5.59 (2H, s), 7.11 (1H, dt, J=1, 8Hz), 7.20-7.26 (2H, m), 7.34 (1H, d, J=8Hz), 7.46 (1H, dd, J=1, 8Hz), 7.60 (1H, t, J=5Hz), 7.66 (1H, dd, J=1, 8Hz), 7.73 (1H, s), 7.88 (1H, s)
mp : 134-135°C

²⁵ Example 17 (Reference example)

[0161] The following compounds were formed in the same manner as in Example 15.

Example 17-1 (Reference example)

³⁰ 1-(2-Chlorobenzyl)-2-cyclopropyl-6-(2-pyridylcarbamoyl)-benzimidazole (68)

[0162] Properties of Compound (68):

³⁵ ¹H-NMR (CDCl₃, δ) : 1.16 (2H, m), 1.32 (2H, m), 1.92 (1H, m), 5.61 (2H, s), 6.57 (1H, d, J=7.5 and 1.5Hz), 7.15 (1H, dt, J=7.5 and 1.5Hz), 7.22-7.31 (2H, m), 7.48 (1H, dd, J=7.5 and 1.5Hz), 7.77 (1H, d, J=9Hz), 8.05 (2H, m).
mp : 206-209°C

⁴⁰ Example 17-2 (Reference example)

6-(2-Carboxy-1-pyrrolidinocarbonyl)-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (69)

[0163] Properties of Compound (69):

⁴⁵ ¹H-NMR (DMSO-d6, δ) : 0.92 (3H, t, J=7.5Hz), 1.65-1.99 (5H, m), 2.25 (1H, m), 2.77 (2H, t, J=7.5Hz), 3.50 (2H, m), 4.40 (1H, m), 5.52 (2H, s), 6.53 (1H, d, J=7.5Hz), 7.21-7.71 (6H, m).
mp : 96°C

⁵⁰ Example 17-3 (Reference example)

1-(2-Chlorobenzyl)-2-cyclobutyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (70)

[0164] Properties of Compound (70):

⁵⁵ ¹H-NMR (CDCl₃, δ) : 1.90-2.21 (2H, m), 2.25-2.37 (2H, m), 2.40-2.65 (2H, m), 3.64 (1H, m), 4.76 (2H, d, J=5Hz), 5.39 (2H, s), 6.33 (1H, d, J=7.5Hz), 7.05 (1H, t, J=7.5Hz), 7.16-7.26 (2H, m), 7.33 (1H, d, J=7.5Hz), 7.46 (1H, d, J=7.5Hz), 7.69-7.76 (3H, m), 7.73 (1H, d, J=7.5Hz), 7.86 (1H, s), 8.55 (1H, d, J=5Hz).
mp : 183-185°C.

Example 17-4 (Reference example)

(1-(2-Chlorobenzyl)-2-n-propyl-5-[(2-pyridylmethyl)carbamoyl]-benzimidazole (71)

5 [0165] Properties of Compound (71):

¹H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=7.5Hz), 1.90 (2H, m), 2.80 (2H, t, J=7.5Hz), 4.80 (2H, d, J=5Hz), 5.44 (2H, s),
 6.40 (1H, d, J=7.5Hz), 7.09 (1H, t, J=7.5Hz), 7.21-7.27 (3H, m), 7.34 (1H, d, J=7.5Hz), 7.47 (1H, d, J=7.5Hz),
 7.64-7.72 (2H, m), 7.83 (1H, dd, J=7.5 and 2Hz), 8.30 (1H, d, J=2Hz), 8.56 (1H, d, J=5Hz).

10 mp : 115-116°C

Example 17-5 (Reference example)

15 1-(2-Chlorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)carbamoyl]-2-n-propylbenzimidazole (72)

[0166] Properties of Compound (72):

¹H-NMR (DMSO-d6, δ) : 1.03 (3H, t, J=7.5Hz), 1.87 (2H, m), 2.79 (2H, t, J=7.5Hz), 3.05 (3H, brs), 4.60 (1H, brs),
 4.87 (1H, brs), 5.40 (2H, d, J=unknown), 6.38 (1H, d, J=unknown), 7.05 (1H, brs), 7.20 (3H, m), 7.35-7.49 (3H,
 20 m), 7.60-7.81 (2H, m), 8.54 (1H, brs).
 mp : 99°C.

Example 17-6 (Reference example)

25 1-(2-Chlorobenzyl)-6-piperonylcaramoyl-2-n-propylbenzimidazole (73)

[0167] Properties of Compound (73):

¹H-NMR (CDCl₃, δ) : 1.01 (3H, t, J=7.5Hz), 1.88 (2H, m), 2.78 (2H, t, J=7.5Hz), 4.54 (2H, d, J=5Hz), 5.45 (2H, s),
 5.95 (2H, s), 6.36 (1H, d, J=7.5Hz), 6.44 (1H, t, J=5Hz), 6.75-6.85 (3H, m), 7.08 (1H, t, J=7.5Hz), 7.23 (1H, t,
 J=7.5Hz), 7.45 (1H, d, J=7.5Hz), 7.67 (1H, dd, J=7.5, 2Hz), 7.78 (1H, d, J=7.5Hz), 7.83 (1H, s).
 mp : 131-134°C.

Example 17-7 (Reference example)

35 1-(2-chlorobenzyl)-6-phenylcarbamoyl-2-n-propylbenzimidazole (74)

[0168] Properties of Compound (74):

¹H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=7.5Hz), 1.90 (2H, m), 2.81 (2H, t, J=7.5Hz), 5.47 (2H, s), 6.40 (1H, d, J=7.5Hz),
 7.06-7.18 (2H, m), 7.26 (1H, t, J=7.5Hz), 7.35 (2H, t, J=7.5Hz), 7.48 (1H, d, J=7.5Hz), 7.64 (2H, d, J=7.5Hz), 7.72
 (1H, dd, J=7.5 and 2Hz), 7.85-7.95 (3H, m).
 mp : 168°C.

45 Example 17-8 (Reference example)

1-(2-Chlorobenzyl)-2-n-propyl-6-[(4-pyridylmethyl)carbamoyl]-benzimidazole (75)

[0169] Properties of Compound (75):

¹H-NMR (DMSO-d6, δ) : 0.93 (3H, t, J=7.5Hz), 1.76 (2H, m), 2.78 (2H, t, J=7.5Hz), 4.49 (2H, d, J=5Hz), 6.42 (1H,
 d, J=7.5Hz), 7.22 (1H, t, J=7.5Hz), 7.27 (2H, d, J=7.5Hz), 7.34 (1H, t, J=7.5Hz), 7.57 (1H, d, J=7.5Hz), 7.69 (1H,
 d, J=7.5Hz), 7.80 (1H, d, J=7.5Hz), 7.97 (1H, s), 8.48 (2H, d, J=7.5Hz), 9.03 (1H, t, J=5Hz).
 mp : 170-173°C.

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Example 17-9 (Reference example)

1-(2-Chlorobenzyl)-2-n-propyl-6-[(3-pyridylmethyl)carbamoyl]-benzimidazole (76)

5 [0170] Properties of Compound (76):

¹H-NMR (DMSO-d₆, δ) : 0.95 (3H, t, J=7.5Hz), 1.76 (2H, m), 2.80 (2H, t, J=7.5Hz), 4.50 (2H, d, J=5Hz), 5.60 (2H, s), 6.42 (1H, d, J=7.5Hz), 7.23 (1H, t, J=7.5Hz), 7.30-7.58 (2H, m), 7.57 (1H, d, J=7.5Hz), 7.67-7.74 (2H, m), 7.75 (1H, d, J=7.5Hz), 7.97 (1H, s), 8.46 (1H, d, J=5Hz), 8.56 (1H, s), 9.0 (1H, t, J=5Hz).
10 mp : 193-195°C.

Example 17-10 (Reference example)

1-(2-Chlorobenzyl)-6-[N-methyl-N-(2-pyridyl)carbamoyl]-2-n-propylbenzimidazole (77)

15 [0171] Properties of Compound (77):

¹H-NMR (DMSO-d₆, δ) : 0.90 (3H, t, J=7.5Hz), 1.70 (2H, m), 2.73 (2H, t, J=7.5Hz), 3.40 (3H, s), 5.42 (2H, s), 6.23 (1H, d, J=7.5Hz), 6.91 (1H, d, J=7.5Hz), 6.98 (1H, m), 7.15-7.25 (3H, m), 7.36 (1H, t, J=7.5Hz), 7.46-7.57 (3H, m), 8.23 (1H, m).
20 mp : 143-146°C.

Example 17-11 (Reference example)

25 1-(2-Chlorobenzyl)-6-(homopiperidinocarbonyl)-2-n-propylbenzimidazole (78)

[0172] Properties of Compound (78):

¹H-NMR (CDCl₃, δ) : 1.03 (3H, t, J=7.5Hz), 1.46-1.94 (10H, m), 2.80 (2H, t, J=7.5Hz), 3.32 (2H, brs), 3.64 (2H, t, J=7.5Hz), 5.41 (2H, s), 6.42 (1H, d, J=7.5Hz), 7.07 (1H, t, J=7.5Hz), 7.19-7.29 (3H, m), 7.45 (1H, d, J=7.5Hz), 7.76 (1H, d, J=7.5Hz).
30 mp : 136-137°C.

Example 17-12 (Reference example)

35 1-(3-Methylbenzyl)-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (79)

[0173] Properties of Compound (79):

¹H-NMR (CDCl₃, δ) : 1.02 (3H, t, J=7.5Hz), 1.88 (2H, m), 2.26 (3H, s), 2.81 (2H, t, J=7.5Hz), 4.76 (2H, d, J=5Hz), 5.36 (2H, s), 6.78-6.84 (2H, m), 7.07 (1H, d, J=7.5Hz), 7.13-7.22 (2H, m), 7.33 (1H, d, J=7.5Hz), 7.57-7.72 (2H, m), 7.78 (1H, d, J=7.5Hz), 7.94 (1H, s), 8.55 (1H, d, J=5Hz).
40 mp : 129-131°C.

Example 17-13 (Reference example)

2-n-Butyl-1-(2-fluorobenzyl)-6-[N-methyl-N-(2-pyridylmethyl)-carbamoyl]benzimidazole (80)

45 [0174] Properties of Compound (80):

¹H-NMR (CDCl₃, δ) : 0.92 (3H, t, J=7.5Hz), 1.45 (2H, m), 1.83 (2H, m), 2.86 (2H, t, J=7.5Hz), 3.06 (3H, brs), 4.61 (1H, brs), 4.86 (1H, brs), 5.37 (2H, brd), 6.62 (1H, brd), 6.97 (1H, brs), 7.07-7.85 (8H, m), 8.57 (1H, d, J=5Hz).
50 mp : 97-100°C.

Example 17-14 (Reference example)

1-(2-Chlorobenzyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (81)

5 [0175] Properties of Compound (81):

¹H-NMR (CDCl₃, δ) : 1.43 (3H, t, J=7.5Hz), 2.84 (2H, q, J=7.5Hz), 4.76 (2H, d, J=5Hz), 5.45 (2H, s), 6.37 (1H, d, J=7.5Hz), 7.07 (1H, t, J=7.5Hz), 7.19-7.28 (2H, m), 7.33 (1H, d, J=7.5Hz), 7.45 (1H, dd, J=7.5 and 2Hz), 7.62-7.75 (3H, m), 7.82 (1H, d, J=7.5Hz), 7.89 (1H, d, J=2Hz), 8.55 (1H, d, J=5Hz).
10 mp : 167-168°C.

Example 17-15 (Reference example)

2-n-Butyl-1-(2-chlorobenzyl)-7-[(2-pyridylmethyl)carbamoyl]-benzimidazole (82)

15 [0176] Properties of Compound (82):

¹H-NMR (CDCl₃, δ) : 0.93 (3H, t, J=7.5Hz), 1.42 (2H, m), 1.83 (2H, m), 2.81 (2H, t, J=7.5Hz), 4.44 (2H, d, J=5Hz), 5.70 (2H, s), 6.13 (1H, dd, J=7.5 and 2Hz), 6.85-6.97 (3H, m), 7.12-7.28 (4H, m), 7.34 (1H, d, J=7.5Hz), 7.62 (1H, dt, J=7.5 and 2Hz), 7.88 (1H, d, J=7.5Hz), 8.40 (1H, d, J=5Hz).
20 mp : 112-114°C.

Example 17-16 (Reference example)

25 2-Cyclopropyl-1-(2-fluorobenzyl)-6-(piperonylcaramoyl)-benzimidazole (83)

[0177] Properties of Compound (83):

¹H-NMR (DMSO-d6, δ) : 1.05 (4H, m), 2.27 (1H, m), 4.38 (2H, d, J=5Hz), 5.71 (2H, s), 5.98 (2H, s), 6.73-6.91 (4H, m), 7.14 (1H, t, J=7.5Hz), 7.27 (1H, t, J=7.5Hz), 7.36 (1H, m), 7.55 (1H, d, J=7.5Hz), 7.73 (1H, dd, J=7.5 and 2Hz), 8.04 (1H, s), 8.87 (1H, t, J=5Hz).
30 mp : 170-173°C.

Example 17-17 (Reference example)

35 2-[[1-(2-chlorobenzyl)-2-ethylbenzimidazol-6-yl]carbonylaminomethyl]-pyridine-1-oxide (84)

[0178] Properties of Compound (84):

¹H-NMR (CDCl₃, δ) : 1.42 (3H, t, J=7.5Hz), 2.82 (2H, q, J=7.5Hz), 4.81 (2H, d, J=7.5Hz), 5.43 (2H, s), 6.31 (1H, d, J=7.5Hz), 7.06 (1H, t, J=7.5Hz), 7.20-7.31 (3H, m), 7.44 (1H, d, J=7.5Hz), 7.52 (1H, dd, J=7.5 and 2Hz), 7.65 (1H, dd, J=7.5 and 2Hz), 7.77-7.83 (2H, m), 7.96 (1H, t, J=7.5Hz), 8.23 (1H, dd, J=7.5 and 2Hz).
40 mp : 204-207°C

45 Example 17-18 (Reference example)

2-n-Butyl-1-(2-fluorobenzyl)-6-(2-pyridylmethylcarbamoyl) benzimidazole (85)

50 [0179] Properties of Compound (85):

¹H-NMR (CDCl₃, δ) : 0.92 (3H, t, J=7.5Hz), 1.38-1.49 (2H, m), 1.77-1.88 (2H, m), 2.86 (2H, t, J=7.5Hz), 4.78 (2H, d, J=5Hz), 5.46 (2H, s), 6.67 (1H, t, J=9Hz), 7.00 (1H, t, J=9Hz), 7.13 (1H, t, J=9Hz), 7.19-7.31 (2H, m), 7.33 (1H, d, J=9Hz), 7.60 (1H, br peak), 7.65-7.74 (2H, m), 7.79 (1H, d, J=9Hz), 7.97 (1H, d, J=2Hz), 8.58 (1H, d, J=5Hz).
55 mp : 154-155°C

Example 18 (Reference example)

Synthesis of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (86)

- 5 [0180] Two-hundred milligrams of 6-carboxy-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were suspended in 5 ml of tert-butyl alcohol, and 0.19 ml of diphenylphosphorylazide and 0.21 ml of diisopropylethylamine were added thereto at room temperature. The reaction mixture was refluxed for 4 hours, and was then separated with ethyl acetate and with water. The organic layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed and purified through column chromatography using a mixture of ethyl acetate and hexane (at a ratio of from 1:10 to 1:3), and was further recrystallized from a mixture of ethyl acetate and hexane to give 165 mg of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (86).
- 10 [0181] Properties of Compound (86):

colorless crystals.

15 $^1\text{H-NMR}$ (CDCl_3 , δ) : 0.98 (3H, t, $J=8\text{Hz}$), 1.50 (9H, s), 1.86 (2H, sextet, $J=8\text{Hz}$), 2.72 (2H, t, $J=8\text{Hz}$), 5.38 (2H, s), 6.40 (1H, dd, $J=1, 8\text{Hz}$), 6.95 (1H, dd, $J=1, 10\text{Hz}$), 7.08 (1H, dt, $J=1, 8\text{Hz}$), 7.24 (1H, dt, $J=1, 8\text{Hz}$), 7.28 (1H, d, $J=1\text{Hz}$), 7.45 (1H, dd, $J=1, 8\text{Hz}$), 7.66 (1H, d, $J=10\text{Hz}$).
mp : 166-168°C.

Example 19 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-6-cyano-2-n-propylbenzimidazole (87)

- 25 [0182] A solution of 1 mol of titanium tetrachloride in 0.14 ml of dichloromethane and 0.36 ml of triethylamine were added to a solution of 200 mg of 6-carbamoyl-1-(2-chlorobenzyl)-2-n-propylbenzimidazole in 4 ml of tetrahydrofuran at 0°C, and the mixture was stirred at 20°C for 2 hours. The reaction mixture was separated with ethyl acetate and with water. The organic layer was washed with water, dried, and then concentrated under reduced pressure. The residue was developed and purified through column chromatography using a mixture of ethyl acetate and hexane (at a ratio of from 1:10 to 1:3), and was further recrystallized from a mixture of ethyl acetate and hexane to give 140 mg of 1-(2-chlorobenzyl)-6-cyano-2-n-propylbenzimidazole (87).
- 30 [0183] Properties of Compound (87):

colorless crystals.

35 $^1\text{H-NMR}$ (CDCl_3 , δ) : 1.05 (3H, t, $J=8\text{Hz}$), 1.90 (2H, sextet, $J=8\text{Hz}$), 2.85 (2H, t, $J=8\text{Hz}$), 5.45 (2H, s), 6.42 (1H, dd, $J=1, 8\text{Hz}$), 7.15 (1H, dt, $J=1, 8\text{Hz}$), 7.28 (1H, dt, $J=1, 8\text{Hz}$), 7.48 (1H, s), 7.50 (1H, d, $J=10\text{Hz}$), 7.54 (1H, dd, $J=1, 8\text{Hz}$), 7.85 (1H, d, $J=10\text{Hz}$).
mp : 124-126°C.

Example 20

Synthesis of 1-(2-chlorobenzyl)-6-mesylamino-2-n-propylbenzimidazole (88)

- 40 [0184] 1-(2-Chlorobenzyl)-2-n-propylbenzimidazole (150 mg) and 61 mg of triethylamine were dissolved in 3 ml of methylene chloride, and 70 mg of methanesulfonyl chloride were added thereto at room temperature. The mixture was stirred for 1 hour, then washed with dilute hydrochloric acid, washed with water, and dried. The solvent was distilled off under reduced pressure. The residual solid was collected with ether through filtration to give 124 mg of 1-(2-chlorobenzyl)-6-mesylamino-2-n-propylbenzimidazole (88).
- 45 [0185] Properties of Compound (88):

50 $^1\text{H-NMR}$ ($\text{CDCl}_3-\text{CD}_3\text{OD}$, δ) : 0.94 (3H, t, $J=7.5\text{Hz}$), 1.76 (2H, m), 2.71 (2H, t, $J=7.5\text{Hz}$), 2.81 (3H, s), 5.36 (2H, s), 6.40 (1H, d, $J=7.5\text{Hz}$), 6.98-7.22 (4H, m), 7.40 (1H, d, $J=7.5\text{Hz}$), 7.59 (1H, d, $J=7.5\text{Hz}$)
mp : 191-193°C.

Example 21 (Reference example)

Synthesis of 6-acetylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (89)

- 55 [0186] Acetic anhydride (62 mg) was added to a solution of 150 mg of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenz-

imidazole and 61 mg of triethylamine in 3 ml of methylene chloride at room temperature, and the mixture was stirred for 1 hour. The reaction mixture was washed with water, and was then dried. The solvent was distilled off under reduced pressure. The residue was crystallized with ether to give 143 mg of 6-acetylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (89).

5 [0187] Properties of Compound (89):

¹H-NMR (CDCl₃, δ) : 1.00 (3H, t, J=7.5Hz), 1.86 (2H, m), 2.17 (3H, s), 2.73 (2H, t, J=7.5Hz), 5.39 (2H, s), 6.43 (1H, d, J=7.5Hz), 6.98-7.11 (2H, m), 7.22 (1H, t, J=7.5Hz), 7.45 (1H, d, J=7.5Hz), 7.59 (1H, brs), 7.68 (1H, d, J=7.5Hz), 7.84 (1H, d, J=1.5Hz).
10 mp : 180-182°C.

Example 22 (Reference example)

Synthesis of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (90)

15 [0188] Seven-hundred milligrams of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole were dissolved in a mixed solvent of 10 ml of methylene chloride and 1 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for 5 hours. A small amount of methylene chloride was added to the reaction solution. The mixture was washed with a sodium carbonate aqueous solution, and was dried. The solvent was then distilled off. The residue was crystallized from a mixed solvent of n-hexane and ether to give 455 mg of 6-amino-1-(2-chlorobenzyl)-2-n-propylbenzimidazole (90).

20 [0189] Properties of Compound (90):

¹H-NMR (CDCl₃, δ) : 1.01 (3H, t, J=7.5Hz), 1.86 (2H, m), 2.73 (2H, t, J=7.5Hz), 5.30 (2H, s), 6.41 (1H, d, J=1.5Hz), 25 6.48 (1H, d, J=7.5Hz), 6.66 (1H, dd, J=7.5 and 1.5Hz), 7.10 (1H, t, J=7.5Hz), 7.25 (1H, t, J=7.5Hz), 7.46 (1H, d, J=7.5Hz), 7.57 (1H, d, J=7.5Hz).
mp : 121-122°C.

Example 23 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-n-propyl-6-ureidobenzimidazole (91)

[0190] 1-(2-Chlorobenzyl)-2-n-propyl-6-ureidobenzimidazole (91) was formed in the same manner as in Example 21.
[0191] Properties of Compound (91):

35 ¹H-NMR (DMSO-d6, δ) : 0.93 (3H, t, J=7.5Hz), 1.72 (2H, m), 2.73 (2H, t, J=7.5Hz), 5.43 (2H, s), 5.73 (2H, s), 6.42 (1H, dd, J=7.5 and 1.5Hz), 7.05 (1H, dd, J=7.5 and 1.5Hz), 7.22 (1H, dt, J=7.5 and 1.5Hz), 7.33 (1H, dt, J=7.5 and 1.5Hz), 7.45 (1H, d, J=7.5Hz), 7.50 (1H, s), 7.57 (1H, dd, J=7.5 and 1.5Hz), 8.50 (1H, s).
mp : 198°C

40 Production Example 12

Production of ethyl 3-acetylamino-4-nitrobenzoate

45 [0192] Nine milliliters of acetyl chloride were added to a mixture of 18.4 g of ethyl 3-amino-4-nitrobenzoate and 200 ml of N,N-dimethylaniline while being cooled with ice. The mixture was stirred at room temperature for 2 hours and then at 50°C for 2 hours. The reaction solution was poured into cold 1-N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with 1-N hydrochloric acid and then with water, and was dried. The solvent was then distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to give 19.6 g of ethyl 3-acetylamino-4-nitrobenzoate.

50 [0193] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 1.42(3H, t, J=7.1Hz), 2.32(3H, s), 4.43(2H, q, J=7.1Hz), 7.82(1H, dd, J=1.8 and 8.7Hz), 8.25 (1H, d, J=8.7Hz), 9.35(1H, d, J=1.8Hz), 10.19(1H, s).

Production Example 13

Production of ethyl 4-nitro-3-phenylacetylaminobenzoate

5 [0194] In the same manner as in Production Example 12, 3.30 g of ethyl 4-nitro-3-phenylacetylaminobenzoate were formed from 2.02 g of ethyl 3-amino-4-nitrobenzoate and 1.87 g of phenylacetyl chloride.

[0195] Properties of the compound:

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.41(3\text{H}, \text{t}, J=7.2\text{Hz}), 3.85(2\text{H}, \text{s}), 4.42(2\text{H}, \text{q}, J=7.2\text{Hz}), 7.34-7.49(5\text{H}, \text{m}), 7.79(1\text{H}, \text{m}), 8.19(1\text{H}, \text{d}, J=8.7\text{Hz}), 9.39(1\text{H}, \text{d}, J=1.6\text{Hz}), 10.15(1\text{H}, \text{s}).$

Production Example 14

Production of ethyl 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzoate

15 [0196] To a solution of 1.706 g of ethyl 3-acetylamino-4-nitrobenzoate in 12 ml of N,N-dimethylformamide were added 0.406 g of 60% sodium hydride while being cooled with ice, and the mixture was stirred at room temperature for 40 minutes. A solution of 1.806 g of 2-chlorobenzyl bromide in 10 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into cold 1-N hydrochloric acid, and the mixed solution was extracted twice with ethyl acetate. The organic layer was washed with 1-N hydrochloric acid and then with water, and was dried. The solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to give 2.08 g of oily ethyl 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzoate.

[0197] Properties of the compound:

25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.38(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.92(3\text{H}, \text{s}), 4.28-4.45(2\text{H}, \text{m}), 4.72(1\text{H}, \text{d}, J=14.5\text{Hz}), 5.34(1\text{H}, \text{d}, J=14.5\text{Hz}), 7.16-7.44(4\text{H}, \text{m}), 7.69(1\text{H}, \text{d}, J=1.7\text{Hz}), 7.94(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.13(1\text{H}, \text{dd}, J=1.7 \text{ and } 8.4\text{Hz}).$

Production Example 15

Production of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)benzyl]-acetylamino]benzoate

30 [0198] In the same manner as in Production Example 14, 1.82 g of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)benzyl]-acetylamino]benzoate were formed from 1.49 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.69 g of 2-(trifluoromethyl)benzyl bromide.

[0199] Properties of the compound:

35 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.37(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.96(3\text{H}, \text{s}), 4.29-4.42(2\text{H}, \text{m}), 4.78(1\text{H}, \text{d}, J=15.4\text{Hz}), 5.40(1\text{H}, \text{d}, J=15.4\text{Hz}), 7.38(1\text{H}, \text{t}, J=7.6\text{Hz}), 7.51-7.58(2\text{H}, \text{m}), 7.61(1\text{H}, \text{d}, J=1.7\text{Hz}), 7.67(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.92(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.13(1\text{H}, \text{dd}, J=1.7 \text{ and } 8.4\text{Hz}).$
mp : 153.5-158.0°C.

Production Example 16

45 Production of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)benzyl]-acetylaminobenzoate

[0200] In the same manner as in Production Example 14, 1.52 g of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)benzyl]-acetylaminobenzoate were formed from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.71 g of 4-(trifluoromethyl)benzyl bromide.

50 [0201] Properties of the compound:

40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.36(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.91(3\text{H}, \text{s}), 4.32-4.43(2\text{H}, \text{m}), 4.42(1\text{H}, \text{d}, J=14.6\text{Hz}), 5.33(1\text{H}, \text{d}, J=14.6\text{Hz}), 7.30(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.54(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.61(1\text{H}, \text{d}, J=1.8\text{Hz}), 7.96(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.12(1\text{H}, \text{dd}, J=1.8 \text{ and } 8.4\text{Hz})$

55

Production Example 17

Production of 2-cyanobenzyl 3-[N-(2-cyanobenzyl)acetylarnino]-4-nitrobenzoate

- 5 [0202] A solution of 1.50 g of 3-acetylarnino-4-nitrobenzoic acid in 10 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.802 g of 60 % sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. Subsequently, a solution of 3.93 g of 2-cyanobenzyl bromide in 10 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was stirred for 30 minutes. Ethyl acetate was poured into the reaction solution, and the crystals precipitated were separated through filtration. The crystals obtained were washed with ethyl acetate, and were further dissolved in chloroform. The filtrate from which the solid component was removed was concentrated to give 1.96 g of yellow crystals of 2-cyanobenzyl 3-[N-(2-cyanobenzyl)acetylarnino]-4-nitrobenzoate.
- 10 [0203] Properties of the compound:

15 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 1.92(3H, s), 4.92(1H, d, $J=4.8\text{Hz}$), 5.24(2H, d, $J=4.9\text{Hz}$), 5.44(2H, dd, $J=7.9$ and 2.9Hz), 7.36(1H, t, $J=7.5\text{Hz}$), 7.47(1H, d, $J=7.7\text{Hz}$), 7.52(1H, t, $J=7.7\text{Hz}$), 7.56-7.62(2H, m), 7.63-7.71(2H, m), 7.76(1H, d, $J=7.8\text{Hz}$), 7.80(1H, d, $J=1.7\text{Hz}$), 7.99(1H, d, $J=8.4\text{Hz}$), 8.25(1H, dd, $J=8.4$ and 1.8Hz).

Production Example 18

Production of ethyl 4-amino-3-(N-i-propylbutyrylarnino)benzoate

- 20 [0204] A solution of 2.00 g of ethyl 3-butyrylarnino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.428 g of 60% sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. A solution of 1.46 g of isopropyl iodide in 10 ml of N,N-dimethylformamide was then added dropwise thereto, and the mixture was stirred at 100°C for 5 days. The reaction solution was poured into a mixed solution of 80 g of dilute hydrochloric acid and 80 g of ethyl acetate for separation. The resulting organic layer was washed with 50 g of water, and was then concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 4:1) to obtain 0.260 g of crude ethyl 4-nitro-3-(N-i-propylbutyrylarnino)benzoate. Subsequently, 3 ml of ethanol and 2 ml of acetic acid were added to 0.260 g of ethyl 4-nitro-3-(N-i-propylbutyrylarnino)benzoate at room temperature, and 0.519 g of reduced iron were further added thereto. The mixture was heat-refluxed for 4 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated. To the residue were added 30 ml of ethyl acetate and 30 ml of dilute hydrochloric acid for separation. The organic layer was washed with 30 ml of water, and was then concentrated under reduced pressure. The residue was purified through preparative thin-layer silica-gel chromatography (developing eluent: a mixture of hexane and ethyl acetate at a ratio of 1:1) to give 0.06 g of ethyl 4-amino-3-(N-i-propylbutyrylarnino)benzoate.
- 25 [0205] Properties of the compound:

30 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 0.82(3H, t, $J=7.4\text{Hz}$), 1.01(3H, d, $J=6.9\text{Hz}$), 1.24(3H, d, $J=6.6\text{Hz}$), 1.38(3H, t, $J=7.0\text{Hz}$), 1.54-1.62(2H, m), 1.87-2.04(2H, m), 4.34(2H, q, $J=7.0\text{Hz}$), 4.45(2H, s), 4.88-4.96(1H, m), 6.78(1H, d, $J=8.4\text{Hz}$), 7.64(1H, d, $J=1.9\text{Hz}$), 7.87(1H, dd, $J=8.4$ and 1.9Hz).

Production example 19

45 Production of ethyl 3-nitro-4-phenylacetylarninobenzoate

- [0206] In the same manner as in Production example 12, 6.00 g of ethyl 3-nitro-4-phenylacetylarninobenzoate were formed from 4.04 g of ethyl 4-amino-3-nitrobenzoate and 3.74 g of phenylacetyl chloride.

50 Production Example 20

Production of N-benzenesulfonyl-3-amino-4-nitrobenzamide

- 55 [0207] N,N'-carbonyldiimidazole (28.9 g) was added to a solution of 20.0 g of 3-acetylarnino-4-nitrobenzoic acid in 300 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Further, 28.00 g of benzenesulfonamide and 27.16 g of diazabicycloundecene were added thereto, and the mixture was stirred at 100°C for 4 days. The solvent was distilled off under reduced pressure. Chloroform and a 10% sodium hydroxide aqueous solution were added to the residue, and the mixture was vigorously stirred. The aqueous layer was neutralized with

10% hydrochloric acid, and the mixture was vigorously stirred with the addition of chloroform. The crystals precipitated were separated through filtration, and were dried to 14.4 g of N-benzenesulfonyl-3-amino-4-nitrobenzamide.

[0208] Properties of the compound:

5 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 6.93(1\text{H, dd, } J=1.8 \text{ and } 9.0\text{Hz}), 7.43(1\text{H, d, } J=1.8\text{Hz}), 7.52(2\text{H, br s}), 7.65(2\text{H, t, } J=7.5\text{Hz}),$
 7.74(1H, t, J=7.5Hz), 7.98-7.82(3H, m), 12.74(1H, s).

Production Example 21

10 Production of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt

15 **[0209]** To a solution of 10.0 g of N-benzenesulfonyl-3-amino-4-nitrobenzamide in 150 ml of methanol were added 56.5 g of a 20% potassium hydrogencarbonate aqueous solution and 11.5 g of 4-bromomethylbiphenyl, and the mixture was stirred at 70°C for 3 hours. The mixture was cooled, and the crystals precipitated were collected through filtration, and were dried to give 4.27 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt.

[0210] Properties of the compound:

19 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.65(2\text{H, d, } J=5.8\text{Hz}), 7.19(1\text{H, d, } J=8.9\text{Hz}), 7.33-7.42(4\text{H, m}), 7.57-7.71(4\text{H, m}), 7.75-7.81(2\text{H, m}), 8.02(1\text{H, d, } J=8.9\text{Hz}), 8.61(1\text{H, br t}).$
 20 IR(Nujol) : 1598cm $^{-1}$.

Production Example 22

25 Production of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide potassium salt

30 **[0211]** Five-percent palladium on carbon (0.64 g) was added to a mixture containing 4.27 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-nitrobenzamide potassium salt, 10.7 g of a 20% potassium hydrogencarbonate aqueous solution and 200 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 35°C for 14 hours. The crystals precipitated were dissolved in 400 ml of a mixed solution of acetone and water (at a ratio of 5:2). The solid material was separated through filtration. The filtrate was concentrated, and the crystals precipitated were separated through filtration, and were dried to give 3.15 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)-benzamide potassium salt.

[0212] Properties of the compound:

35 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.31(2\text{H, d, } J=5.7\text{Hz}), 4.85(2\text{H, s}), 4.91(1\text{H, br t, } J=5.7\text{Hz}), 6.45(1\text{H, d, } J=7.9\text{Hz}), 7.07(1\text{H, s}), 7.13(1\text{H, d, } J=7.9\text{Hz}), 7.29-7.36(4\text{H, m}), 7.43-7.47(4\text{H, m}), 7.60(2\text{H, d, } J=8.1\text{Hz}), 7.65(2\text{H, d, } J=7.6\text{Hz}), 7.73-7.76(2\text{H, m}).$
 IR(Nujol) : 1574cm $^{-1}$.

40 Production Example 23

Production of N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide

45 **[0213]** Oxalyl chloride (1.25 g) was added dropwise to a solution of 1.00 g of 4-acetylamino-3-nitrobenzoic acid and 0.20 g of N,N-dimethylformamide in 15 ml of methylene chloride while being cooled with ice. The mixture was further stirred at room temperature for 1 hour. The reaction solution was concentrated, and diisopropyl ether was added thereto for crystallization. The crystals were added to a solution of 0.483 g of 2-aminomethylpyridine and 0.35 g of triethylamine in 15 ml of methylene chloride. After the mixture was stirred at room temperature for 1 hour, the organic layer was washed twice with water (100 ml x 2) and then with 100 ml of a sodium hydrogencarbonate aqueous solution. The organic layer was concentrated to give 0.99 g of N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide.

[0214] Properties of the compound:

55 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.33(3\text{H, s}), 4.76(2\text{H, d, } J=4.8\text{Hz}), 7.25(1\text{H, dd, } J=5.0 \text{ and } 7.2\text{Hz}), 7.34(1\text{H, d, } J=7.9\text{Hz}), 7.71(1\text{H, dt, } J=1.8 \text{ and } 7.8\text{Hz}), 7.84(1\text{H, s}), 8.14(1\text{H, dd, } J=2.1 \text{ and } 8.8\text{Hz}), 8.58(1\text{H, d, } J=4.9\text{Hz}), 8.77(1\text{H, d, } J=2.1\text{Hz}), 8.90(1\text{H, d, } J=8.0\text{Hz}), 10.47(1\text{H, s}).$

Production Example 24

Production of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide

5 [0215] Five-percent palladium on carbon (2.53 g) was added to a solution of 10.0 g of N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide in 150 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 60°C for 15 hours. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 7:3) to give 8.02 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide.

10 [0216] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 2.06(3H, s), 4.52(2H, d, J=5.9Hz), 5.09(2H, s), 7.10(1H, dd, J=1.9 and 8.2Hz), 7.22-7.30(3H, m), 7.38(1H, d, J=8.2Hz), 7.75(1H, dt, J=1.7 and 7.6Hz), 8.50(1H, d, J=4.6Hz), 8.84(1H, t, J=5.8Hz), 9.19(1H, s).

15

Production Example 25

Production of N-(2-pyridylmethyl)-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide

20 [0217] To a solution of 0.80 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10 ml of N,N-dimethylformamide were added 1.31 g of 4-benzyloxybenzyl chloride and 1.18 g of sodium hydrogencarbonate, and the mixture was stirred at 90 °C for 2 hours. Chloroform and water were added to the reaction solution, and the chloroform extraction was conducted. The organic layer was washed with water, concentrated, and purified through silica-gel column chromatography to give 0.434 g of N-(2-pyridylmethyl)-4-acetylamino-3-(4-benzyloxybenzylamino)benzamide.

25 [0218] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 2.07(3H, s), 4.30(2H, d, J=5.6Hz), 4.51(2H, d, J=5.9Hz), 5.07(2H, s), 5.68(1H, t, J=5.6Hz), 6.97(2H, d, J=8.6Hz), 7.14(2H, m), 7.25(2H, dd, J=3.4 and 7.4Hz), 7.32(4H, t, 7.5Hz), 7.38(2H, t, J=7.1Hz), 7.44(2H, d, J=7.2Hz), 7.72(1H, dt, J=1.8 and 7.7Hz), 8.49(1H, dd, J=1.9 and 5.3Hz), 8.89(1H, t, J=5.9Hz), 9.28(1H, s).

30

Production Example 26

Production of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide

35 [0219] To a solution of 0.80 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10ml of N,N-dimethylformamide were added 0.962 g of 3,4-methylenedioxybenzyl chloride and 0.710 g of sodium hydrogencarbonate, and the mixture was stirred at 80°C for 4 hours. Chloroform and water were added to the reaction solution, and the chloroform extraction was conducted. The organic layer was washed with water, concentrated, and purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.49 g of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide.

40 [0220] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 2.08(3H, s), 4.29(2H, s), 4.52(2H, d, J=5.9Hz), 5.27(1H, s), 5.97(2H, s), 6.84-6.88(2H, m), 6.96(1H, s), 7.10(1H, d, J=1.3Hz), 7.13(1H, dd, J=1.6 and 8.2Hz), 7.25-7.32(3H, m), 7.76(1H, dt, J=1.2 and 7.6Hz), 8.51(1H, d, J=4.8Hz), 8.90(1H, t, J=5.8Hz), 9.28(1H, s).

45

Production Example 27

Production of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide

50 [0221] To a solution of 0.800 g of N-(2-pyridylmethyl)-4-acetylamino-3-aminobenzamide in 10 ml of methanol were added 1.08 g of 4-(4-bromomethylphenyl)-1,2,3-thiadiazole and 0.710 g of sodium hydrogencarbonate, and the mixture was stirred at 70°C for 1 hour. The reaction solution was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.830 g of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide

55 [0222] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 2.11(3H, s), 4.43-5.56(2H, m), 5.92(1H, t, J=5.9Hz), 7.51(1H, d, J=1.4Hz), 7.15(1H, dd, J=1.6

and 8.1Hz), 7.22(2H, dd, J=1.9 and 8.1Hz), 7.33(1H, d, J=8.1Hz), 7.57(2H, d, J=8.1Hz), 7.69(1H, dt, J=1.8 and 7.7Hz), 8.09(2H, d, J=8.2Hz), 8.47(1H, dd, J=1.9 and 5.2Hz), 8.89(1H, t, J=5.9Hz), 9.34(1H, s), 9.58(1H, s).

Production Example 28

[0223] N,N'-carbonyldiimidazole (14.45 g) was added to a solution of 10.00 g of 4-acetylamino-3-nitrobenzoic acid in 300 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, 14.03 g of benzenesulfonamide and 13.58 g of diazabicycloundecene were added thereto, and the mixture was stirred at 100°C for 72 hours. The reaction mixture was separated with the addition of chloroform and water. The organic layer was then concentrated, and the resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 12.67 g of N-benzenesulfonyl-4-acetylamino-3-nitrobenzamide.

[0224] Properties of the compound:

¹H-NMR(DMSO-d6, δ) : 2.08(3H, s), 7.39-7.47(3H, m), 7.65(1H, d, J=8.5Hz), 7.84(2H, dd, J=1.4 and 7.7Hz), 8.11(1H, dd, J=1.9 and 8.4Hz), 8.38(1H, d, J=1.9Hz), 10.34(1H, s).

Production Example 29

Production of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide

[0225] N-benzenesulfonyl-4-acetylamino-3-nitrobenzamide (12.67 g) was dissolved in 200 ml of methanol and 30 ml of water, and 7.59 g of potassium hydrogencarbonate were further added thereto. The mixture was hydrogenated in a hydrogen atmosphere using 2.53 g of 5% palladium on carbon as catalyst at 40°C for 24 hours. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 6.72 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide.

[0226] Properties of the compound:

¹H-NMR(DMSO-d6, δ) : 2.06(3H, s), 7.07(1H, dd, J=1.8 and 8.3Hz), 7.17(1H, d, J=1.8Hz), 7.44(1H, d, J=8.3Hz), 7.61(2H, t), 7.68(1H, t), 7.96(2H, d, J=7.5Hz), 9.19(1H, s).
IR(Nujol) : 1682cm⁻¹.

Production Example 30

Production of N-benzenesulfonyl-4-acetylamino-3-(2-nitrobenzylamino)benzamide

[0227] In the same manner as in Production Example 32, 0.79 g of N-benzenesulfonyl-4-acetylamino-3-(2-nitrobenzylamino)benzamide were formed from 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.52 g of 2-nitrobenzyl bromide.

[0228] Properties of the compound:

¹H-NMR(DMSO-d6, δ) : 2.08(3H, s), 4.72(2H, d, J=5.0Hz), 5.92(1H, s), 6.86(1H, s), 7.13(1H, d, J=8.1Hz), 7.31(1H, d, J=8.0Hz), 7.49-7.58(3H, m), 7.60(2H, d, J=7.6Hz), 7.66(1H, t, J=7.4Hz), 7.86(2H, d, J=7.7Hz), 8.11(1H, d, J=8.3Hz), 9.37(1H, s).

Production Example 31

Production of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide

[0229] In the same manner as in Production Example 32, 0.38 g of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide were formed from 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.47 g of benzyl bromide.

[0230] Properties of the compound:

¹H-NMR (DMSO-d6, δ) : 2.07 (3H, s), 4.35(2H, d, J=5.5Hz), 5.73(1H, s), 7.06(1H, s), 7.14(1H, d, J=8.3Hz),

7.21-7.28(2H, m), 7.32(2H, t, J=7.3Hz), 7.37(2H, d, J=7.6Hz), 7.53(2H, t, J=7.4Hz), 7.59(1H, t, J=7.0Hz), 7.88(2H, d, J=7.7Hz), 9.29(1H, s), 12.34(1H, s)

5 Production Example 32

Production of N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)benzamide

[0231] A solution of 7ml of methanol containing 0.60 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide, 0.656 g of 2,4-difluorobenzyl bromide and 0.423 g of potassium hydrogencarbonate was stirred at 60°C for 1 hour. The reaction solution was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.370 g of N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)-benzamide.

[0232] Properties of the compound:

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.05(3\text{H}, \text{s}), 4.34(2\text{H}, \text{d}, J=5.5\text{Hz}), 5.60(1\text{H}, \text{s}), 7.02(1\text{H}, \text{t}, J=8.0\text{Hz}), 7.06(1\text{H}, \text{s}), 7.16-7.27(3\text{H}, \text{m}), 7.38-7.51(4\text{H}, \text{m}), 7.82(2\text{H}, \text{d}, J=7.2\text{Hz}), 9.27(1\text{H}, \text{s}), 12.35(1\text{H}, \text{s})$

20 Production Example 33

Production of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide

[0233] In the same manner as in Production Example 32, 0.52 g of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide were formed from 0.50 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.436 g of 4-nitrobenzyl bromide.

[0234] Properties of the compound:

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.09(3\text{H}, \text{s}), 4.54(2\text{H}, \text{d}, J=5.0\text{Hz}), 6.10(1\text{H}, \text{s}), 6.89(1\text{H}, \text{d}, J=1.8\text{Hz}), 7.14(1\text{H}, \text{dd}, J=1.8 \text{ and } 8.2\text{Hz}), 7.39(1\text{H}, \text{d}, J=8.2\text{Hz}), 7.58-7.65(4\text{H}, \text{m}), 7.68(1\text{H}, \text{t}, J=7.6\text{Hz}), 7.92(2\text{H}, \text{dd}, J=1.4 \text{ and } 7.4\text{Hz}), 8.20(2\text{H}, \text{d}, J=8.7\text{Hz}), 9.36(1\text{H}, \text{s}), 12.28(1\text{H}, \text{s})$

35 Production Example 34

Production of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide

[0235] In the same manner as in Production Example 32, 0.38 g of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide were formed from 0.50 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.45 g of 4-(4-bromomethylphenyl)-1,2,3-thiadiazole.

[0236] Properties of the compound:

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.10(3\text{H}, \text{s}), 4.46(2\text{H}, \text{d}, J=5.3\text{Hz}), 5.96(1\text{H}, \text{s}), 7.03(1\text{H}, \text{s}), 7.14(1\text{H}, \text{dd}, J=1.7 \text{ and } 8.2\text{Hz}), 7.40(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.52-7.61(4\text{H}, \text{m}), 7.65(1\text{H}, \text{t}, J=7.1\text{Hz}), 7.93(2\text{H}, \text{d}, J=7.6\text{Hz}), 8.10(2\text{H}, \text{d}, J=8.2\text{Hz}), 9.35(1\text{H}, \text{s}), 9.58(1\text{H}, \text{s}), 12.31(1\text{H}, \text{s})$

45 Production Example 35

Production of ethyl 3-amino-2-nitrobenzoate

[0237] A mixture of 20.2 g of 3-acetylamino-2-nitrobenzoic acid, 11.4 g of 97% sulfuric acid and 300 ml of ethanol was stirred for 23 hours while being heat-refluxed. One-hundred milliliters of ethanol were distilled off under reduced pressure, and the residue was cooled to room temperature. Subsequently, the reaction solution was poured into 200 ml of ice water containing 19.5 g of sodium hydrogencarbonate. The crystals precipitated were separated through filtration, and were washed with water. Further, these crystals were dispersed in 30 ml of a mixed solution of ethyl acetate and hexane at a ratio of 1:2. The crystals were separated through filtration, washed with hexane, and then dried to give 18.0 g of ethyl 3-amino-2-nitrobenzoate.

[0238] Properties of the compound:

1H-NMR(CDCl_3 , δ) : 1.39(3H, t, J=7.1Hz), 4.37(2H, q, J=7.1Hz), 6.41(2H, br s), 6.83(1H, d, J=8.7Hz), 8.00(1H, dd, J=1.8 and 8.7Hz), 8.85(1H, d, J=1.8Hz)

Production Example 36

Production of ethyl 3-acetylamino-2-nitrobenzoate

5 [0239] Acetyl chloride (13 ml) was added dropwise to a solution of 2.98 g of ethyl 3-amino-2-nitrobenzoate and 20 ml of N,N-dimethylaniline in an ice bath. The mixture was stirred at room temperature for 48 hours. The reaction solution was acidified with 10% hydrochloric acid, and was extracted twice with ethyl acetate. The organic layer was washed three times with water. The solvent was distilled off under reduced pressure, and the resulting residue was crystallized with hexane. The crystals were separated through filtration, washed with hexane, and dried to give 3.30 g of ethyl 3-acetylamino-2-nitrobenzoate.

10 [0240] Properties of the compound:

15 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.42(3\text{H}, \text{t}), 2.33(3\text{H}, \text{s}), 4.42(2\text{H}, \text{q}), 8.27(1\text{H}, \text{dd}, J=1.9 \text{ and } 8.9\text{Hz}), 8.89(1\text{H}, \text{d}, J=1.9\text{Hz}),$
 $8.91(1\text{H}, \text{d}, J=8.9\text{Hz}), 10.54(1\text{H}, \text{br s})$

Production Example 37

Production of ethyl 4-acetylamino-3-aminobenzoate .

20 [0241] A mixture of 149.4 g of ethyl 3-acetylamino-2-nitrobenzoate, 14.9g of 5% palladium on carbon and 1,500 ml of ethanol was stirred in a hydrogen atmosphere for 15 hours. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was dissolved in a small amount of ethanol, and diisopropyl ether was added thereto. The crystals precipitated were separated through filtration, and were dried to give 114.4 g of ethyl 4-acetylamino-3-aminobenzoate.

25 [0242] Properties of the compound:

1H-NMR(DMSO-d6, δ) : 1.27(3H, t), 2.05(3H, s), 4.23(2H, q), 5.19(2H, s), 7.13(1H, d, J=8.2Hz), 7.35(1H, s), 7.47(1H, d, J=8.2Hz), 9.19(1H, s)

Example 24 (Reference examples)

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycaibanyl-2-methylbenzimidazole (92)

30 [0243] Twenty milliliters of ethanol, 11 ml of acetic acid and 3.07 g of reduced iron were added to 2.07 g of ethyl 3-[N-(2-chlorobenzyl)acetylamino]-4-nitrobenzoate, and the mixture was refluxed for 4 hours. The solid material was separated through filtration, and was washed with ethanol. The filtrate was concentrated, and a sodium hydrogen carbonate aqueous solution was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was dried, and the solvent was then distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 100:(10 to 70:30) to give 1.46 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92).

35 [0244] Properties of Compound (92):

40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.57(3\text{H}, \text{s}), 4.37(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.46(2\text{H}, \text{s}), 6.41(1\text{H}, \text{d}, J=7.8\text{Hz}),$
 $7.10(1\text{H}, \text{t}, J=7.8\text{Hz}), 7.25(1\text{H}, \text{t}), 7.47(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.75(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.94(1\text{H}, \text{s}), 8.00(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz})$

Example 25 (Reference examples)

Synthesis of 6-ethoxycarbonyl-1-methyl-2-n-propylbenzimidazole (93)

50 [0245] In the same manner as in Production Example 14, 1.00 g of crude ethyl 3-(N-methylbutyrylamino)-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-butyrylamino-4-nitrobenzoate and 0.843 g of methyl iodide. Subsequently, 0.56 g of 6-ethoxycarbonyl-1-methyl-2-n-propylbenzimidazole (93) were formed in the same manner as in Example 24.

55 [0246] Properties of Compound (93):

1H-NMR(CDCl₃, δ) : 1.08(3H, t, J=7.4Hz), 1.43(3H, t, J=7.0Hz), 1.89-1.97(2H, m), 2.89(2H, t, J=7.7Hz), 3.79(3H, s), 4.38-4.44(2H, m), 7.71(1H, d, J=8.4Hz), 7.96(1H, dd, J=8.4 and 1.5Hz), 8.05(1H, d, J=1.4Hz)

Example 26 (Reference examples)

Synthesis of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (94)

- 5 [0247] A solution of 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate in 10 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.428 g of 60% sodium hydride and 10 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred at room temperature for 30 minutes. Subsequently, a solution of 1.97 g of n-butyl iodide in 10 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was heated at 50°C for 13 hours. The reaction solution was poured into a mixed solution of 70 g of dilute hydrochloric acid and 70 g of ethyl acetate for extraction. The resulting organic layer was washed twice with water, dried, and then concentrated under reduced pressure to obtain 2.59 g of crude ethyl 3-(N-n-butylbutyrylamino)-4-nitrobenzoate. Then, 0.81 g of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (94) were formed in the same manner as in Example 24.
- 10 [0248] Properties of Compound (94):

15 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 0.98(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.08(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.43(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.75-1.83(2\text{H}, \text{m}), 1.91-1.98(2\text{H}, \text{m}), 2.88(2\text{H}, \text{t}, J=7.6\text{Hz}), 4.15(2\text{H}, \text{t}, J=7.5\text{Hz}), 4.42(2\text{H}, \text{q}, J=7.2\text{Hz}), 7.73(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.96(1\text{H}, \text{dd}, J=8.5\text{ and }1.5\text{Hz}), 8.06(1\text{H}, \text{d}, J=1.4\text{Hz})$

Example 27 (Reference examples)

Synthesis of 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (95)

- 20 [0249] In the same manner as in Production Example 14, crude ethyl 3-[N-(3-chlorobenzyl)butyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.64 g of 3-chlorobenzyl bromide. This compound was converted to 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole [(95), 0.57 g] in the same manner as in Example 24 without being purified.
- 25 [0250] Properties of Compound (95):

30 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.02(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.39(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.85-1.92(2\text{H}, \text{m}), 2.80(2\text{H}, \text{t}, J=7.5\text{Hz}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.37(2\text{H}, \text{s}), 6.86(1\text{H}, \text{d}, J=7.4\text{Hz}), 7.04(1\text{H}, \text{s}), 7.21-7.29(2\text{H}, \text{m}), 7.77(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.96(1\text{H}, \text{d}, J=1.2\text{Hz}), 7.99(1\text{H}, \text{dd}, J=8.5\text{ and }1.5\text{Hz})$

Example 28 (Reference example)

Synthesis of 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole (96)

- 35 [0251] In the same manner as in Production Example 14, ethyl 3-[N-benzylbutyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.36 g of benzyl bromide. This compound was converted to 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole [(96), 0.97 g] in the same manner as in Example 24 without being purified.
- 40 [0252] Properties of Compound (96):

45 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.01(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.39(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.83-1.91(2\text{H}, \text{m}), 2.81(2\text{H}, \text{t}, J=7.5\text{Hz}), 4.37(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.40(2\text{H}, \text{s}), 7.03(1\text{H}, \text{d}, J=6.4\text{Hz}), 7.28-7.33(3\text{H}, \text{m}), 7.76(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.98(1\text{H}, \text{dd}, J=8.4\text{ and }1.2\text{Hz}), 8.00(1\text{H}, \text{s})$

Example 29 (Reference example)

Synthesis of 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole (97)

- 50 [0253] In the same manner as in Production Example 14, ethyl 3-[N-(4-chlorobenzyl)butyrylamino]-4-nitrobenzoate was obtained from 1.86 g of ethyl 3-butyrylamino-4-nitrobenzoate and 1.64 g of 4-chlorobenzyl bromide. This compound was converted to 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole [(97), 1.06 g] in the same manner as in Example 24 without being purified.
- 55 [0254] Properties of Compound (97):

1H-NMR(CDCl_3, δ) : 1.02(3H, t, J=7.4Hz), 1.39(3H, t, J=7.1Hz), 1.83-1.92(2H, m), 2.80(2H, t, J=7.8Hz), 4.38(2H, q, J=7.5Hz), 5.36(2H, s), 6.96(2H, d, J=8.2Hz), 7.29(2H, d, J=8.3Hz), 7.76(1H, d, J=8.4Hz), 7.96(1H, d, J=1.2Hz),

7.99(1H, dd, J=8.3 and 1.2Hz)

Example 30 (Reference example)

5 Synthesis of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)-benzyl]benzimidazole (98)

[0255] In the same manner as in Example 24, 1.32 g of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl]-benzimidazole (98) were formed from 1.82 g of ethyl 4-nitro-3-[N-[2-(trifluoromethyl)benzyl]acetylamino]benzoate.

[0256] Properties of Compound (98):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.38(3\text{H}, \text{t}, \text{J}=7.1\text{Hz}), 2.53(3\text{H}, \text{s}), 4.37(2\text{H}, \text{q}, \text{J}=7.1\text{Hz}), 5.58(2\text{H}, \text{s}), 6.47(1\text{H}, \text{d}, \text{J}=7.7\text{Hz}), 7.36(1\text{H}, \text{t}, \text{J}=7.5\text{Hz}), 7.41(1\text{H}, \text{t}, \text{J}=7.5\text{Hz}), 7.75\text{--}7.97(2\text{H}, \text{m}), 7.94(1\text{H}, \text{d}, \text{J}=1.0\text{Hz}), 8.02(1\text{H}, \text{dd}, \text{J}=1.6 \text{ and } 8.6\text{Hz})$.

Example 31 (Reference example)

15 Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)-benzyl]benzimidazole (99)

[0257] In the same manner as in Example 24, 1.22 g of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole (99) were formed from 1.52 g of ethyl 4-nitro-3-[N-[4-(trifluoromethyl)benzyl]acetylamino]benzoate.

20 [0258] Properties of Compound (99):

$^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, \text{J}=7.1\text{Hz}), 2.58(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, \text{J}=7.1\text{Hz}), 5.44(2\text{H}, \text{s}), 7.15(2\text{H}, \text{d}, \text{J}=8.2\text{Hz}), 7.59(2\text{H}, \text{d}, \text{J}=8.2\text{Hz}), 7.75(1\text{H}, \text{d}, \text{J}=8.3\text{Hz}), 7.97(1\text{H}, \text{s}), 8.00(1\text{H}, \text{dd}, \text{J}=1.5 \text{ and } 8.5\text{Hz})$

25 Example 32 (Reference example)

Synthesis of 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (100)

30 [0259] In the same manner as in Production Example 14, ethyl 3-[N-(3,4-dichlorobenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.74 g of 3,4-dichlorobenzyl bromide. This compound was converted to 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(100), 0.76 g] in the same manner as in Example 24 without being purified.

[0260] Properties of Compound (100):

35 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, \text{J}=7.1\text{Hz}), 2.58(3\text{H}, \text{s}), 4.39(2\text{H}, \text{q}, \text{J}=7.2\text{Hz}), 5.33(2\text{H}, \text{s}), 6.84(1\text{H}, \text{dd}, \text{J}=8.4 \text{ and } 2.3\text{Hz}), 7.16(2\text{H}, \text{d}, \text{J}=2.0\text{Hz}), 7.39(1\text{H}, \text{d}, \text{J}=8.3\text{Hz}), 7.74(1\text{H}, \text{d}, \text{J}=8.4\text{Hz}), 7.96(1\text{H}, \text{d}, \text{J}=1.2\text{Hz}), 8.00(1\text{H}, \text{dd}, \text{J}=8.4 \text{ and } 1.5\text{Hz})$

Example 33 (Reference example)

40 Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (101)

45 [0261] In the same manner as in Production Example 14, 1.44 g of crude ethyl 3-[N-biphenyl-4-ylmethyl]acetylamino]-4-nitrobenzoate were obtained from 1.51 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.46 g of 4-chloromethylbiphenyl. Subsequently, 1.13 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (101) were formed in the same manner as in Example 24.

[0262] Properties of Compound (101):

50 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, \text{J}=7.1\text{Hz}), 2.62(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, \text{J}=7.1\text{Hz}), 5.42(2\text{H}, \text{s}), 7.11(2\text{H}, \text{d}, \text{J}=8.2\text{Hz}), 7.34(1\text{H}, \text{m}), 7.42(2\text{H}, \text{m}), 7.54(4\text{H}, \text{m}), 7.74(1\text{H}, \text{d}, \text{J}=8.4\text{Hz}), 7.99(1\text{H}, \text{dd}, \text{J}=1.5 \text{ and } 8.4\text{Hz}), 8.06(1\text{H}, \text{d}, \text{J}=1.5\text{Hz})$

Example 34 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)-benzimidazole (102)

55 [0263] In the same manner as in Production Example 14, ethyl 3-[N-(2-methylbenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.65 g of 2-methylbenzyl bromide. This compound was converted to 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)benzimidazole [(102), 0.81 g] in the same manner as

in Example 24 without being purified.

[0264] Properties of Compound (102):

5 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.38(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.43(3\text{H}, \text{s}), 2.54(3\text{H}, \text{s}), 4.36(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.33(2\text{H}, \text{s}), 6.35(1\text{H}, \text{d}, J=7.7\text{Hz}), 7.03(1\text{H}, \text{t}, J=8.2\text{Hz}), 7.18-7.25(2\text{H}, \text{m}), 7.75(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.91(1\text{H}, \text{d}, J=1.2\text{Hz}), 7.98(1\text{H}, \text{dd}, J=8.5\text{ and }1.5\text{Hz})$

Example 35 (Reference example)

10 Synthesis of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole (103)

15 **[0265]** In the same manner as in Production example 14, crude ethyl 3-[N-(2-methoxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.16 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.44 g of 2-methoxybenzyl chloride. Subsequently, 1.18 g of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole (103) were formed in the same manner as in Example 24.

[0266] Properties of Compound (103):

20 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.60(3\text{H}, \text{s}), 3.90(3\text{H}, \text{s}), 4.37(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.36(2\text{H}, \text{s}), 6.61(1\text{H}, \text{d}, J=7.4\text{Hz}), 6.82(1\text{H}, \text{t}, J=7.5\text{Hz}), 6.92(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.27(1\text{H}, \text{m}), 7.71(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.96(1\text{H}, \text{dd}, J=1.5\text{ and }8.4\text{Hz}), 8.03(1\text{H}, \text{d}, J=1.3\text{Hz})$

Example 36 (Reference example)

25 Synthesis of 6-ethoxycarbonyl-1-(4-methoxybeazyl)-2-methylbenzimidazole (104)

30 **[0267]** In the same manner as in Production Example 14, crude ethyl 3-[N-(4-methoxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.60 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.49 g of 4-methoxybenzyl chloride. Subsequently, 1.27 g of 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole (104) were formed in the same manner as in Example 24.

[0268] Properties of Compound (104):

35 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.59(3\text{H}, \text{s}), 3.77(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.31(2\text{H}, \text{s}), 6.84(2\text{H}, \text{m}), 7.00(2\text{H}, \text{m}), 7.71(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.97(1\text{H}, \text{dd}, J=1.4\text{ and }8.4\text{Hz}), 8.03(1\text{H}, \text{d}, J=1.3\text{Hz})$

40 Example 37 (Reference example)

Synthesis of 1-[2-(benzenesulfonylmethyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (105)

45 **[0269]** In the same manner as in Production Example 14, ethyl 3-[N-[2-(benzenesulfonylmethyl)benzyl]acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.93 g of 2-(benzenesulfonylmethyl)benzyl bromide. This compound was converted to 1-[2-benzenesulfonylmethyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole [(105), 0.89 g] in the same manner as in Example 24 without being purified.

[0270] Properties of Compound (105):

50 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.37(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.57(3\text{H}, \text{s}), 4.36(2\text{H}, \text{q}, J=7.1\text{Hz}), 4.50(2\text{H}, \text{s}), 5.60(2\text{H}, \text{s}), 6.38(1\text{H}, \text{d}, J=6.7\text{Hz}), 6.88(1\text{H}, \text{dd}, J=1.5\text{ and }7.3\text{Hz}), 7.10-7.18(2\text{H}, \text{m}), 7.57(2\text{H}, \text{t}, J=7.6\text{Hz}), 7.69-7.78(2\text{H}, \text{m}), 7.79(1\text{H}, \text{dd}, J=0.8\text{ and }8.1\text{Hz}), 7.92(1\text{H}, \text{d}, J=1.2\text{Hz}), 7.99(1\text{H}, \text{dd}, J=1.5\text{ and }8.4\text{Hz})$

Example 38 (Reference example)

55 Synthesis of 1-(2-cyanobenzyl)-6-(2-cyanobenzylloxycarbonyl)-2-methylbenzimidazole (106)

[0271] In the same manner as in Example 24, 1.75 g of 1-(2-cyanobenzyl)-6-(2-cyanobenzylloxycarbonyl)-2-methylbenzimidazole (106) were formed from 3.33 g of 2-cyanobenzyl 3-[N-(2-cyanobenzyl)acetylamino]-4-nitrobenzoate.

[0272] Properties of Compound (106):

60 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.60(3\text{H}, \text{s}), 5.55(2\text{H}, \text{s}), 5.60(2\text{H}, \text{s}), 6.68(1\text{H}, \text{d}, J=7.3\text{Hz}), 7.41-7.48(3\text{H}, \text{m}), 7.61(2\text{H}, \text{m}), 7.72(1\text{H}, \text{d}, J=7.6\text{Hz}), 7.76(1\text{H}, \text{d}, J=7.6\text{Hz}), 7.77(1\text{H}, \text{d}, J=8.6\text{Hz}), 8.02(1\text{H}, \text{s}), 8.05(1\text{H}, \text{dd}, J=8.4\text{ and }1.5\text{Hz})$

Example 39 (Reference example)

Synthesis of 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (107)

5 [0273] In the same manner as in Production Example 14, ethyl 3-[N-(biphenyl-2-ylmethyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.47 g of 2-bromomethylbiphenyl. This compound was converted to 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(107), 1.31 g] in the same manner as in Example 24 without being purified.

[0274] Properties of Compound (107):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.41(3\text{H}, \text{t}, J=7.3\text{Hz}), 2.39(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.3\text{Hz}), 5.27(2\text{H}, \text{s}), 6.68(1\text{H}, \text{d}, J=7.9\text{Hz}), 7.21(1\text{H}, \text{dt}, J=9.0 \text{ and } 2.1\text{Hz}), 7.32-7.39(4\text{H}, \text{m}), 7.43(1\text{H}, \text{dd}, J=7.3 \text{ and } 1.9\text{Hz}), 7.46-7.51(2\text{H}, \text{m}), 7.68(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.87(1\text{H}, \text{d}, J=1.3\text{Hz}), 7.95(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz})$

Example 40 (Reference example)

Synthesis of 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole (108)

20 [0275] In the same manner as in Production Example 14, ethyl 3-(N-benzylacetylamino)-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.02 g of benzyl bromide. This compound was converted to 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole [(108), 0.71 g] in the same manner as in Example 24 without being purified.

[0276] Properties of Compound (108):

25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.58(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.38(2\text{H}, \text{s}), 7.05(2\text{H}, \text{dd}, J=8.3 \text{ and } 1.8\text{Hz}), 7.28-7.33(3\text{H}, \text{m}), 7.72(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.98(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz}), 8.02(1\text{H}, \text{d}, J=1.2\text{Hz})$

Example 41 (Reference example)

30 Synthesis of 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (109)

35 [0277] In the same manner as in Production Example 14, ethyl 3-[N-(4-tert-butylbenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.35 g of 4-tert-butylbenzyl bromide. This compound was converted to crude 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(109), 1.60 g] in the same manner as in Example 24 without being purified.

Example 42 (Reference example)

40 Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)-benzimidazole (110)

45 [0278] In the same manner as in Production example 14, ethyl 3-[N-(2-naphthylmethyl)acetylamino]-4-nitrobenzoate was obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.32 g of 2-naphthylmethyl bromide. This compound was converted to crude 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)benzimidazole [(110), 1.28 g] in the same manner as in Example 24 without being purified.

Example 43 (Reference example)

50 Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole (111)

55 [0279] In the same manner as in Production Example 14, ethyl 3-[N-(biphenyl-4-ylmethyl)propionylamino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 4-nitro-3-propionylaminobenzoate and 2.28 g of 4-chloromethylbiphenyl. This compound was converted to 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole [(111), 2.07 g] in the same manner as in Example 24 without being purified.

[0280] Properties of Compound (111):

55 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, J=7.2\text{Hz}), 1.45(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.90(2\text{H}, \text{q}, J=7.5\text{Hz}), 4.38(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.43(2\text{H}, \text{s}), 7.10(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.33-7.36(1\text{H}, \text{m}), 7.43(2\text{H}, \text{t}, J=7.4\text{Hz}), 7.51-7.56(4\text{H}, \text{m}), 7.79(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.80(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.05(1\text{H}, \text{d}, J=1.3\text{Hz})$

Example 44 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole (112)

5 [0281] In the same manner as in Production Example 14, ethyl 4-[N-(2-chlorobenzyl)acetylamino]-3-nitrobenzoate was obtained from 3.15 g of ethyl 4-acetylamino-3-nitrobenzoate and 3.85 g of 2-chlorobenzyl bromide. This compound was converted to 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole [(112), 2.54 g] in the same manner as in Example 24 without being purified.

10 [0282] Properties of Compound (112):

¹H-NMR(CDCl₃, δ) : 1.41(3H, t, J=7.1Hz), 2.59(3H, s), 4.40(2H, q, J=7.1Hz), 5.43(1H, s), 6.43(1H, d, J=7.8Hz), 7.10(1H, t, J=7.5Hz), 7.19(1H, d, J=8.5Hz), 7.25(1H, m), 7.46(1H, d, J=8.1Hz), 7.95(1H, dd, J=1.4 and 8.4Hz), 8.47(1H, s).

Example 45 (Reference example)

Synthesis of 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (113)

20 [0283] In the same manner as in Production Example 14, ethyl 3-[N-(2,6-dichlorobenzyl)acetylamino]-4-nitrobenzoate was obtained from 1.50 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.14 g of 2,6-dichlorobenzyl bromide. This compound was converted to 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole [(113), 0.91 g] in the same manner as in Example 24 without being purified.

[0284] Properties of Compound (113):

¹H-NMR(CDCl₃, δ) : 1.38(3H, t, J=7.1Hz), 2.64(3H, s), 4.34(2H, q, J=7.1Hz), 5.61(2H, s), 7.30(1H, dd, J=7.6 and 8.5Hz), 7.40(2H, d, J=8.0Hz), 7.66(1H, d, J=8.4Hz), 7.87(1H, d, J=1.1Hz), 7.91(1H, dd, J=8.4 and 1.5Hz).

Example 46 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole (114)

[0285] Two milliliters of acetic acid were added to 0.06 g of ethyl 4-amino-3-(N-i-propylbutyrylamino)benzoate, and the mixture was stirred at 90°C for 14 hours. The reaction solution was concentrated under reduced pressure to give 0.05 g of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole (114).

[0286] Properties of Compound (114):

¹H-NMR(CDCl₃, δ) : 1.07(3H, t, J=7.4Hz), 1.43(3H, t, J=7.0Hz), 1.69(6H, d, J=6.9Hz), 1.85-1.92(2H, m), 2.91(2H, t, J=7.7Hz), 4.41(2H, q, J=7.3Hz), 4.67-4.76(1H, m), 7.72(1H, d, J=8.3Hz), 7.94(1H, dd, J=8.7 and 1.5Hz), 8.25(1H, d, J=1.2Hz)

Example 47 (Reference example)

Synthesis of 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole (115)

45 [0287] To a solution of 0.924 g of ethyl 4-nitro-3-phenylacetylaminobenzoate in 10 ml of N,N-dimethylformamide were added 0.166 g of 60% sodium hydride while being cooled with ice, and the mixture was stirred at room temperature for 1 hour. Methyl iodide (0.50 ml) was added thereto, and the resulting mixture was stirred at room temperature for 1 hour. The reaction solution was poured into cold 1-N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with 1-N hydrochloric acid and then with water, and was dried. The solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (developing eluent: a mixture of ethyl acetate and hexane at a ratio of from 1:10 to 1:4) to obtain 0.510 g of ethyl 4-nitro-3-[N-(methyl)phenylacetylamino] benzoate. To 0.148 g of this compound were added 2 ml of ethanol, 1 ml of acetic acid and 0.240 g of reduced iron, and the mixture was refluxed for 2 hours. The solid material was separated through filtration. The filtrate was concentrated, and was then purified through preparative thin-layer silica-gel chromatography (eluent: a mixture of chloroform and ethyl acetate at a ratio of 2:1) to give 0.090 g of 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole (115).

[0288] Properties of Compound (115):

¹H-NMR(CDCl₃, δ) : 1.41(3H, t, J=7.1Hz), 3.63(3H, s), 4.32(2H, s), 4.40(2H, q, J=7.1Hz), 7.21-7.26(3H, m), 7.27-7.32(2H, m), 7.72(1H, d, J=8.4Hz), 7.98(1H, dd, J=1.5 and 8.4Hz), 8.03(1H, d, J=1.3Hz).

Example 48 (Reference example)

Synthesis of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (116)

[0289] A solution of 1.50 g of ethyl 3-acetylamido-4-nitrobenzoate in 8 ml of N,N-dimethylformamide was added dropwise to a slurry of 0.357 g of 60% sodium hydride and 8 ml of N,N-dimethylformamide at room temperature, and the mixture was stirred for 30 minutes. Subsequently, a solution of 1.74 g of 2,4-dichlorobenzyl chloride in 8 ml of N,N-dimethylformamide was added dropwise thereto, and the mixture was stirred for 30 minutes. The reaction solution was poured into a mixed solution of 50 g of dilute hydrochloric acid and 60 g of ethyl acetate for separation. The resulting organic layer was washed twice with 50 g of water. This organic layer was concentrated under reduced pressure to obtain 3.5 g of crude ethyl 3-[N-(2,4-dichlorobenzyl)acetylamino]-4-nitrobenzoate. This compound without being purified was dissolved in 23 ml of ethanol and 12 ml of acetic acid, and then 3.32 g of reduced iron were added thereto. The mixture was heat-refluxed for 6 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated under reduced pressure. The resulting residue was separated with the addition of 60 ml of ethyl acetate and 50 ml of dilute hydrochloric acid. The organic layer was washed with 50 g of a saturated aqueous solution of sodium hydrogencarbonate and then twice with 50 g of water, and was concentrated under reduced pressure. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 4:1 to 1:1) to give 0.94 g of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (116).

[0290] Properties of Compound (116):

¹H-NMR(CDCl₃, δ) : 1.40(3H, t, J=7.1Hz), 2.56(3H, s), 4.38(2H, q, J=7.1Hz), 5.41(2H, s), 6.34(1H, d, J=8.4Hz), 7.09(1H, dd, J=8.4 and 2.0Hz), 7.49(1H, d, J=2.0Hz), 7.75(1H, d, J=8.4Hz), 7.92(1H, s), 8.00(1H, dd, J=8.5 and 1.4Hz)

Example 49 (Reference example)

Synthesis of 6-carboxy-1-(4-chlorobenzyl)-2-n-propylbenzimidazole (117)

[0291] To 1.06 g of 1-(4-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole were added 3.57 g of a 10% sodium hydroxide aqueous solution, 5 ml of ethanol and 3.57 g of water, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the resulting residue, and the inorganic salt was separated through filtration. The filtrate was concentrated under reduced pressure to obtain 0.80 g of the residue. This residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to give 0.63 g of 6-carboxy-1-(4-chlorobenzyl)-2-n-propylbenzimidazole (117).

[0292] Properties of Compound (117):

¹H-NMR(DMSO-d₆, δ) : 0.96(3H, t, J=7.3Hz), 1.76-1.88(2H, m), 3.10-3.23(2H, m), 5.83(2H, s), 7.27(2H, d, J=8.4Hz), 7.44(2H, d, J=8.4Hz), 7.89(1H, d, J=8.4Hz), 7.89(1H, d, J=8.5Hz), 8.28(1H, s)

Example 50 (Reference example)

Synthesis of 6-carboxy-1-methyl-2-n-propylbenzimidazole (118)

[0293] In the same manner as in Example 49, 0.46 g of 6-carboxy-1-methyl-2-n-propylbenzimidazole (118) were formed from 0.56 g of 6-ethoxycarbonyl-1-methyl-2-n-propylcarbonylbenzimidazole.

[0294] Properties of Compound (118):

¹H-NMR(DMSO-d₆, δ) : 1.00(3H, t, J=7.3Hz), 1.79-1.93(2H, m), 3.06(3H, t, J=7.4Hz), 3.92(3H, s), 7.76(1H, d, J=8.4Hz), 7.97(1H, d, J=8.4Hz), 8.31(1H, s).

Example 51 (Reference example)

Synthesis of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole (119)

5 [0295] In the same manner as in Example 49, 0.045 g of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole (119) were formed from 0.045 g of 6-ethoxycarbonyl-2-n-propyl-1-i-propylbenzimidazole.

[0296] Properties of Compound (119):

10 $^1\text{H-NMR}(\text{CD3OD}, \delta) : 0.98(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.61(6\text{H}, \text{d}, J=6.9\text{Hz}), 1.74\text{--}1.82(2\text{H}, \text{m}), 2.89(2\text{H}, \text{t}, J=7.5\text{Hz}), 3.21\text{--}3.24(2\text{H}, \text{m}), 4.78\text{--}4.83(1\text{H}, \text{m}), 7.51(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.84(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz}), 8.26(1\text{H}, \text{s}).$

Example 52 (Reference example)

Synthesis of 1-n-butyl-6-carboxy-2-n-propylbeazimidazole (120)

15 [0297] In the same manner as in Example 49, 0.60 g of 1-n-butyl-6-carboxy-2-n-propylbenzimidazole (120) were formed from 0.81 g of 1-n-butyl-6-ethoxycarbonyl-2-n-propylbenzimidazole.

[0298] Properties of Compound (120):

20 $^1\text{H-NMR}(\text{DMSO-d6}, \delta) : 1.02(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.17(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.33\text{--}1.41(2\text{H}, \text{m}), 1.70\text{--}1.77(2\text{H}, \text{m}), 1.85\text{--}1.93(2\text{H}, \text{m}), 3.07(2\text{H}, \text{t}, J=7.6\text{Hz}), 4.42(2\text{H}, \text{t}, J=7.4\text{Hz}), 7.78(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.99(1\text{H}, \text{dd}, J=8.5 \text{ and } 1.0\text{Hz}), 8.35(1\text{H}, \text{s}), 13.13(1\text{H}, \text{s})$

Example 53 (Reference example)

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

25 [0299] Eighty milliliters of ethanol and 37 g of a 10% sodium hydroxide aqueous solution were added to 10.0 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was refluxed for 4 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The precipitate was collected, washed with water, and dried under reduced pressure to give 8.30 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

Example 54 (Reference example)

Synthesis of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole (122)

35 [0300] In the same manner as in Example 53, 0.72 g of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole (122) were formed from 0.90 g of 1-(2,6-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

40 [0301] Properties of Compound (122):

$^1\text{H-NMR}(\text{DMSO-d6}, \delta) : 2.60(3\text{H}, \text{s}), 5.71(2\text{H}, \text{s}), 7.46(1\text{H}, \text{t}, J=7.9\text{Hz}), 7.57(3\text{H}, \text{t}, J=8.2\text{Hz}), 7.73(2\text{H}, \text{m}), 12.57(1\text{H}, \text{s}).$

Example 55 (Reference example)

Synthesis of 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl]-benzimidazole (123)

45 [0302] In the same manner as in Example 53, 0.98 g of 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl]-benzimidazole (123) were formed from 1.17 g of 6-ethoxycarbonyl-2-methyl-1-[2-(trifluoromethyl)benzyl]-benzimidazole.

[0303] Properties of Compound (123):

$^1\text{H-NMR}(\text{DMSO-d6}, \delta) : 2.49(3\text{H}, \text{s}), 5.70(2\text{H}, \text{s}), 6.46\text{--}6.51(1\text{H}, \text{m}), 7.51(2\text{H}, \text{m}), 7.65(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{dd}, J=1.4 \text{ and } 8.4\text{Hz}), 7.82\text{--}7.87(1\text{H}, \text{m}), 7.91(1\text{H}, \text{s}).$

Example 56 (Reference example)

Synthesis of 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole (124)

- 5 [0304] In the same manner as in Example 53, 1.07 g of 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole (124) were formed from 1.22 g of 6-ethoxycarbonyl-2-methyl-1-[4-(trifluoromethyl)benzyl]-benzimidazole.
 [0305] Properties of Compound (124):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.85(3\text{H}, \text{s}), 5.92(2\text{H}, \text{s}), 7.50(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.74(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.88(1\text{H}, \text{d}, J=8.5\text{Hz}),$
 $8.07(1\text{H}, \text{d}, J=8.5\text{Hz}), 8.31(1\text{H}, \text{s}), 13.3(1\text{H}, \text{br s}).$

Example 57 (Reference example)

Synthesis of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole (125)

- 15 [0306] In the same manner as in Example 53, 0.55 g of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole (125) were formed from 0.76 g of 1-(3,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.
 [0307] Properties of Compound (125):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.56(3\text{H}, \text{s}), 5.61(2\text{H}, \text{s}), 6.98(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.9\text{Hz}), 7.46(1\text{H}, \text{d}, J=1.9\text{Hz}), 7.59(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.63(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.4\text{Hz}), 8.07(1\text{H}, \text{s}), 12.76(1\text{H}, \text{s})$

Example 58 (Reference example)

25 Synthesis of 1-benzyl-6-carboxy-2-n-propylbenzimidazole (126)

- [0308] A 10% sodium hydroxide aqueous solution (3.61 g), 5 ml of ethanol and 3 ml of water were added to 0.97 g of 1-benzyl-6-ethoxycarbonyl-2-n-propylbenzimidazole, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the residue, and the inorganic salt was separated through filtration. The filtrate was concentrated under reduced pressure to give 0.85 g of 1-benzyl-6-carboxy-2-n-propylbenzimidazole (126).
 [0309] Properties of Compound (126):

35 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.94(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.73-1.81(2\text{H}, \text{m}), 2.85(2\text{H}, \text{t}, J=7.3\text{Hz}), 5.59(2\text{H}, \text{s}), 7.07(2\text{H}, \text{dd}, J=1.1 \text{ and } 8.3\text{Hz}), 7.27(1\text{H}, \text{t}, J=7.3\text{Hz}), 7.33(2\text{H}, \text{t}, J=7.4\text{Hz}), 7.65(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.04(1\text{H}, \text{s})$

Example 59 (Reference example)

40 Synthesis of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole (127)

- [0310] In the same manner as in Example 58, 0.35 g of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole (127) were formed from 0.57 g of 1-(3-chlorobenzyl)-6-ethoxycarbonyl-2-n-propylbenzimidazole.
 [0311] Properties of Compound (127):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.94(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.70-1.79(2\text{H}, \text{m}), 2.83(2\text{H}, \text{t}, J=7.4\text{Hz}), 5.59(2\text{H}, \text{s}), 6.94(1\text{H}, \text{s}), 7.15(1\text{H}, \text{s}), 7.34(2\text{H}, \text{d}, J=4.4\text{Hz}), 7.59(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{d}, J=8.1\text{Hz}), 8.02(1\text{H}, \text{s})$

Example 60 (Reference example)

50 Synthesis of 6-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole (128)

- [0312] In the same manner as in Example 58, 0.35 g of 6-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole (128) were formed from 0.61 g of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)-benzimidazole.
 [0313] Properties of Compound (128):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.51(3\text{H}, \text{s}), 5.96(2\text{H}, \text{s}), 6.33(1\text{H}, \text{d}, J=7.0\text{Hz}), 7.55-7.62(2\text{H}, \text{m}), 7.66(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.81(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.06(1\text{H}, \text{s}), 8.24(1\text{H}, \text{d}, J=7.0\text{Hz}), 12.66(1\text{H}, \text{s})$

Example 61 (Reference example)

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

5 [0314] Ethanol (15 ml) and 10.6 g of a 5% sodium hydroxide aqueous solution were added to 1.456 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was refluxed for 1 hour. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The precipitate was collected, washed with water, and dried under reduced pressure to give 0.645 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

10 Example 62 (Reference example)

Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (129)

15 [0315] A 10% sodium hydroxide aqueous solution (3.10 g) and 10 ml of ethanol were added to 0.94 g of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole, and the mixture was heat-refluxed for 1 hour. The reaction solution was adjusted to a pH of 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.68 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (129).

[0316] Properties of Compound (129):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.52(3\text{H}, \text{s}), 5.61(2\text{H}, \text{s}), 6.54(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.33(1\text{H}, \text{dd}, J=8.4 \text{ and } 2.1\text{Hz}), 7.64(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.74(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.81(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz}), 7.98(1\text{H}, \text{s}), 12.72(1\text{H}, \text{s}).$

Example 63 (Reference example)

25 Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole (130)

[0317] In the same manner as in Example 53, 0.83 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole (130) were formed from 1.10 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

[0318] Properties of Compound (130):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.53(3\text{H}, \text{s}), 5.61(2\text{H}, \text{s}), 7.18(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.34(1\text{H}, \text{m}), 7.43(2\text{H}, \text{m}), 7.62(5\text{H}, \text{m}), 7.79(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.5\text{Hz}), 8.09(1\text{H}, \text{d}, J=1.0\text{Hz}), 12.72(1\text{H}, \text{br s})$

Example 64 (Reference example)

35 Synthesis of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole (131)

[0319] In the same manner as in Example 53, 0.55 g of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole (131) were formed from 1.34 g of 1-(4-tert-butylbenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

40 [0320] Properties of Compound (131):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.22(9\text{H}, \text{s}), 2.57(3\text{H}, \text{s}), 5.52(2\text{H}, \text{s}), 7.03(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.35(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.60(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.78(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz}), 8.06(1\text{H}, \text{s}), 12.71(1\text{H}, \text{s})$

45 Example 65 (Reference example)

Synthesis of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole (132)

50 [0321] In the same manner as in Example 53, 0.49 g of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole (132) were formed from 0.81 g of 6-ethoxycarbonyl-2-methyl-1-(2-methylbenzyl)-benzimidazole.

[0322] Properties of Compound (132):

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.41(3\text{H}, \text{s}), 2.48(3\text{H}, \text{s}), 5.55(2\text{H}, \text{s}), 6.14(1\text{H}, \text{d}, J=7.6\text{Hz}), 7.02(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.17(1\text{H}, \text{t}, J=7.3\text{Hz}), 7.26(1\text{H}, \text{d}, J=7.4\text{Hz}), 7.65(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.4\text{Hz}), 7.97(1\text{H}, \text{d}, J=1.1\text{Hz}), 12.71(1\text{H}, \text{s})$

Example 66 (Reference example)

Synthesis of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole (133)

- 5 [0323] In the same manner as in Example 53, 1.00 g of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole (133) was formed from 1.63 g of 6-ethoxycarbonyl-1-(2-methoxybenzyl)-2-methylbenzimidazole.
 [0324] Properties of Compound (133):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.55(3\text{H, s}), 3.81(3\text{H, s}), 5.42(2\text{H, s}), 6.77(1\text{H, m}), 6.85(1\text{H, m}), 7.05(1\text{H, m}), 7.28(1\text{H, m}),$
 $7.58(1\text{H, m}), 7.76(1\text{H, m}), 7.99(1\text{H, s}), 12.65(1\text{H, br s}).$

Example 67 (Reference example)

Synthesis of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole (134)

- 15 [0325] In the same manner as in Example 53, 0.99 g of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole (134) were formed from 1.27 g of 6-ethoxycarbonyl-1-(4-methoxybenzyl)-2-methylbenzimidazole.
 [0326] Properties of Compound (134):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.86(3\text{H, s}), 3.71(3\text{H, s}), 5.69(2\text{H, s}), 6.92(2\text{H, d, J=8.4Hz}), 7.27(2\text{H, d, J=8.4Hz}), 7.84$
 $(1\text{H, d, J=8.5Hz}), 8.04(1\text{H, d, J=8.5Hz}), 8.33(1\text{H, s}), 13.25(1\text{H, br t})$

Example 68 (Reference example)

25 Synthesis of 6-carboxy-2-methyl-1-[2-(benzenesulfonylmethyl) benzyl]benzimidazole (135)

- [0327] In the same manner as in Example 53, 0.74 g of 6-carboxy-2-methyl-1-[2-(benzenesulfonylmethyl)benzyl]-benzimidazole (135) were formed from 0.89 g of 6-ethoxycarbonyl-2-methyl-1-[2-(benzenesulfonylmethyl)benzyl]benzimidazole.

30 [0328] Properties of Compound (135):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.44(3\text{H, s}), 4.99(2\text{H, s}), 5.71(2\text{H, s}), 6.08(1\text{H, d, J=6.5Hz}), 7.12-7.20(3\text{H, m}), 7.64-7.70$
 $(3\text{H, m}), 7.77-7.83(2\text{H, m}), 7.89(2\text{H, s}), 7.90(1\text{H, s}), 12.71(1\text{H, s})$

Example 69 (Reference example)

Synthesis of 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole (136)

- 40 [0329] In the same manner as in Example 53, 1.14 g of 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole (136) were formed from 2.04 g of 1-(2-cyanobenzyl)-6-(2-cyanobenzyloxycarbonyl)-2-methylbenzimidazole.
 [0330] Properties of Compound (136):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.54(3\text{H, s}), 5.80(2\text{H, s}), 6.78(1\text{H, d, J=7.8Hz}), 7.51(1\text{H, t, J=7.4Hz}), 7.61(1\text{H, dt, J=7.8}$
 $\text{and 1.2Hz}), 7.64(1\text{H, d, J=8.4Hz}), 7.80(1\text{H, dd, J=8.4 and 1.5Hz}), 7.94(1\text{H, d, J=6.7Hz}), 8.00(1\text{H, d, J=1.1Hz}),$
 $12.70(1\text{H, s})$

Example 70 (Reference example)

Synthesis of 6-carboxy-1-(biphenyl-2-ylmethyl)-2-methylbenzimidazole (137)

- 50 [0331] In the same manner as in Example 53, 1.07 g of 6-carboxy-1-(biphenyl-2-ylmethyl)-2-methylbenzimidazole (137) were formed from 1.31 g of 1-(biphenyl-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole.
 [0332] Properties of Compound (137):

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.32(3\text{H, s}), 5.45(2\text{H, s}), 6.61(1\text{H, d, J=7.7Hz}), 7.26(1\text{H, dt, J=7.7 and 1.4Hz}), 7.31(1\text{H, dd, J=7.5 and 1.3Hz}), 7.36(1\text{H, dt, J=7.5 and 0.7Hz}), 7.40-7.46(1\text{H, m}), 7.46-7.52(4\text{H, m}), 7.57(1\text{H, d, J=8.4Hz}),$
 $7.76(1\text{H, dd, J=7.9 and 1.5Hz}), 7.86(1\text{H, d, J=1.2Hz}), 12.72(1\text{H, s})$

Example 71 (Reference example)

Synthesis of 1-benzyl-6-carboxy-2-methylbenzimidazole (138)

5 [0333] In the same manner as in Example 53, 0.59 g of 1-benzyl-6-carboxy-2-methylbenzimidazole(138) were formed from 0.71 g of 1-benzyl-6-ethoxycarbonyl-2-methylbenzimidazole.

[0334] Properties of Compound (138):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.56(3\text{H}, \text{s}), 5.57(2\text{H}, \text{s}), 7.11(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.27(1\text{H}, \text{t}, J=7.2\text{Hz}), 7.32-7.35(2\text{H}, \text{m}), 7.61(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.79(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.3\text{Hz}), 8.06(1\text{H}, \text{s}), 12.75(1\text{H}, \text{s})$

Example 72 (Reference example)

Synthesis of 6-carboxy-2-methyl-1-(2-naphthylmethyl)-benzimidazole (139)

15 [0335] In the same manner as in Example 53, 0.80 g of 6-carboxy-2-methyl-1-(2-naphthylmethyl)benzimidazole (139) were formed from 1.28 g of 6-ethoxycarbonyl-2-methyl-1-(2-naphthylmethyl)benzimidazole.

[0336] Properties of Compound (139):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.61(3\text{H}, \text{s}), 5.74(2\text{H}, \text{s}), 7.29(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.46-7.52(2\text{H}, \text{m}), 7.59(1\text{H}, \text{s}), 7.63(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.78-7.92(4\text{H}, \text{m}), 8.09(1\text{H}, \text{s}), 12.68(1\text{H}, \text{s})$.

Example 73 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole (140)

[0337] In the same manner as in Example 53, 1.70 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole (140) were formed from 2.07 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-ethylbenzimidazole.

[0338] Properties of Compound (140):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.32(3\text{H}, \text{t}, J=7.4\text{Hz}), 2.94(2\text{H}, \text{q}, J=7.5\text{Hz}), 5.63(2\text{H}, \text{s}), 7.16(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.34(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.60-7.78(5\text{H}, \text{m}), 7.81(1\text{H}, \text{dd}, J=1.4 \text{ and } 8.4\text{Hz}), 8.10(1\text{H}, \text{d}, J=1.2\text{Hz}), 12.73(1\text{H}, \text{s})$.

Example 74 (Reference example)

Synthesis of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (141)

40 [0339] In the same manner as in Example 53, 2.48 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (141) were formed from 3.70 g of 1-(2-chlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole.

[0340] Properties of Compound (141):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.49(3\text{H}, \text{s}), 5.57(2\text{H}, \text{s}), 6.53(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.22(1\text{H}, \text{t}, J=7.6\text{Hz}), 7.33(1\text{H}, \text{t}, J=7.6\text{Hz}), 7.44(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.54(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.77(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.5\text{Hz}), 8.16(1\text{H}, \text{d}, J=1.3\text{Hz}), 12.71(1\text{H}, \text{br s})$.

Example 75 (Reference example)

Synthesis of 5-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole (142)

50 [0341] In the same manner as in Example 53, 0.15 g of 5-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole (142) were formed from 0.26 g of 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)-benzimidazole.

[0342] Properties of Compound (142):

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.49(3\text{H}, \text{s}), 5.91(2\text{H}, \text{s}), 6.36(1\text{H}, \text{dd}, J=7.2 \text{ and } 1.8\text{Hz}), 7.52(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.55-7.62(2\text{H}, \text{m}), 7.77(1\text{H}, \text{dd}, J=8.5 \text{ and } 1.5\text{Hz}), 8.18(1\text{H}, \text{d}, J=1.3\text{Hz}), 8.24(1\text{H}, \text{dd}, J=7.4 \text{ and } 1.6\text{Hz}), 12.69(1\text{H}, \text{s})$.

Example 76 (Reference example)

Synthesis of 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole (143)

5 [0343] In the same manner as in Example 53, 0.488 g of 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole (143) were formed from 0.635 g of 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole.

[0344] Properties of Compound (143):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.27(2\text{H}, \text{s}), 5.57(2\text{H}, \text{s}), 6.27(1\text{H}, \text{d}, J=7.1\text{Hz}), 7.06(1\text{H}, \text{t}), 7.10-7.29(6\text{H}, \text{m}), 7.39(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.47(1\text{H}, \text{d}, J=7.9\text{Hz}), 7.78(1\text{H}, \text{dd}, J=1.4 \text{ and } 8.6\text{Hz}), 8.21(1\text{H}, \text{d}, J=1.2\text{Hz}), 12.71(1\text{H}, \text{br s})$.

Example 77 (Reference example)

Synthesis of 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole (144)

15 [0345] In the same manner as in Example 53, 0.780 g of 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole (144) were formed from 1.00 g of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole.

[0346] Properties of Compound (144):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.29(2\text{H}, \text{s}), 5.63(2\text{H}, \text{s}), 6.28(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.07(1\text{H}, \text{t}, J=7.6\text{Hz}), 7.15(1\text{H}, \text{m}), 7.19-7.29(5\text{H}, \text{m}), 7.49(1\text{H}, \text{d}, J=7.4\text{Hz}), 7.70(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.91(1\text{H}, \text{s}), 12.73(1\text{H}, \text{br s})$.

Example 78 (Reference example)

Synthesis of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)-benzimidazole (145)

25 [0347] In the same manner as in Example 53, 0.40 g of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (145) were formed from 0.50 g of 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole.

[0348] Properties of Compound (145):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.28(2\text{H}, \text{s}), 5.55(2\text{H}, \text{s}), 6.19(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.08-7.22(6\text{H}, \text{m}), 7.41(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.62(1\text{H}, \text{d}, J=2.2\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.6\text{Hz}), 8.22(1\text{H}, \text{s}), 12.72(1\text{H}, \text{br s})$

Example 79 (Reference example)

Synthesis of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)-benzimidazole (146)

35 [0349] In the same manner as in Example 53, 0.35 g of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole (146) were formed from 0.48 g of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole.

[0350] Properties of Compound (146):

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.30(2\text{H}, \text{s}), 5.61(2\text{H}, \text{s}), 6.19(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.09-7.22(6\text{H}, \text{m}), 7.64(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.71(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.82(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 7.94(1\text{H}, \text{d}, J=1.2\text{Hz}), 12.78(1\text{H}, \text{br s})$

Example 80 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole (147)

45 [0351] In the same manner as in Example 53, 0.483 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole (147) were formed from 0.690 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole.

[0352] Properties of Compound (147):

50 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 5.87(2\text{H}, \text{s}), 7.18(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.60-7.67(4\text{H}, \text{m}), 7.98(2\text{H}, \text{d}, J=0.7\text{Hz}), 8.32(1\text{H}, \text{s}), 13.15(1\text{H}, \text{s})$

Example 81 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole (148)

5 [0353] In the same manner as in Example 53, 0.270 g of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole (148) were formed from 0.38 g of 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole.

[0354] Properties of Compound (148):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 5.80(2\text{H}, \text{s}), 7.19(2\text{H}, \text{d}, J=6.3\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.2\text{Hz}), 7.43(2\text{H}, \text{t}, J=7.3\text{Hz}), 7.82(1\text{H}, \text{d}, J=8.7\text{Hz}), 8.04(1\text{H}, \text{d}, J=8.7\text{Hz}), 8.45(1\text{H}, \text{s})$

Example 82 (Reference example)

Synthesis of 5-ethoxycarbonyl-2-methylbenzimidazole (149)

15 [0355] Reduced iron (6.46 g), 48 ml of ethanol and 24 ml of acetic acid were added to 3.00 g of ethyl 3-acetylaminonitrobenzoate, and the mixture was heat-refluxed for 12 hours. The solid material was removed using a filtration aid, and the filtrate was concentrated under reduced pressure. To the residue were added 100 ml of ethanol and 5.2 g of 35% hydrochloric acid, and the mixture was heat-refluxed for 5 hours. The reaction solution was neutralized with 6.3 g of sodium hydrogencarbonate, and was filtrated. The filtrate was concentrated under reduced pressure. The residue was separated with the addition of 70 ml of ethyl acetate and 70 ml of water. The organic layer was washed three times with water, and the aqueous layer was extracted three times with ethyl acetate. The resulting organic layer was concentrated under reduced pressure to give 1.53 g of a powder of 5-ethoxycarbonyl-2-methylbenzimidazole (149).

20 [0356] Properties of Compound (149):

25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.41(3\text{H}, \text{t}, J=6.9\text{Hz}), 2.67(3\text{H}, \text{s}), 4.40(2\text{H}, \text{q}, J=7.1\text{Hz}), 7.55(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.96(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.5\text{Hz}), 8.27(1\text{H}, \text{d}, J=1.4\text{Hz})$

Example 83 (Reference example)

Synthesis of 2-benzyl-5-ethoxycarbonylbenzimidazole (150)

30 [0357] A mixture of 3.60 g of ethyl 3-nitro-4-phenylacetylaminobenzoate, 47 ml of ethanol, 23 ml of acetic acid and 6.4 g of reduced iron was heat-refluxed for 4 hours. The solid material was separated through filtration, and the filtrate was concentrated. To the residue were added 50 ml of ethanol and 5 g of 35% hydrochloric acid. The mixture was stirred for 40 hours while being heat-refluxed. The reaction solution was neutralized with sodium hydrogencarbonate, and was extracted with chloroform. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography to give 2.30 g of 2-benzyl-5-ethoxycarbonylbenzimidazole (150).

35 [0358] Properties of Compound (150):

40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.39(3\text{H}, \text{t}, J=7.1\text{Hz}), 4.26(2\text{H}, \text{s}), 4.37(2\text{H}, \text{q}, J=7.1\text{Hz}), 7.22-7.36(5\text{H}, \text{m}), 7.50(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.94(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.6\text{Hz}), 8.23(1\text{H}, \text{d}, J=1.3\text{Hz})$

Examples 84 and 85 (Reference examples)

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)-benzimidazole (151) and 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (152)

45 [0359] To 1.00 g of 5-ethoxycarbonyl-2-methylbenzimidazole were added 15 ml of N,N-dimethylformamide, 1.59 g of 2-nitrobenzyl bromide and 1.23 g of sodium hydrogencarbonate, and the mixture was heated at 60 °C for 1 hour. The reaction solution was separated with the addition of 70 ml of ethyl acetate and 70 ml of water. The organic layer was then washed three times with water, and the aqueous layer was extracted three times with ethyl acetate. The resulting organic layer was concentrated under reduced pressure to obtain a mixture of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole and 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole. The mixture was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 1:4 to 0:100) to give 0.614 g of 6-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (151) and 0.259 g of 5-ethoxycarbonyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (152).

55 [0360] Properties of Compound (151):

¹H-NMR(CDCl₃, δ) : 1.38(3H, t, J=7.2Hz), 2.56(3H, s), 4.37(2H, q, J=7.1Hz), 5.84(2H, s), 6.41(1H, d, J=6.8Hz), 7.44-7.53(2H, m), 7.78(1H, d, J=8.6Hz), 7.88(1H, s), 8.02(1H, dd, J=8.3 and 1.5Hz), 8.30(1H, dd, J=7.9 and 1.5Hz)

[0361] Properties of Compound (152):

¹H-NMR(CDCl₃, δ) : 1.42(3H, t, J=7.0Hz), 2.56(3H, s), 4.40(2H, q, J=7.0Hz), 5.80(2H, s), 6.43(1H, dd, J=7.6 and 1.0Hz), 7.14(1H, d, J=8.3Hz), 7.45-7.53(2H, m), 7.95(1H, dd, J=8.4 and 1.5Hz), 8.27(1H, dd, J=8.0 and 1.7Hz), 8.48(1H, d, J=1.2Hz)

Examples 86 and 87 (Reference examples)

Synthesis of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole (153) and 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole (154)

[0362] In the same manner as in Examples 84 and 85, 1.06 g of 2-benzyl-1-(2-chlorobenzyl)-6-ethoxycarbonylbenzimidazole (153) and 0.640 g of 2-benzyl-1-(2-chlorobenzyl)-5-ethoxycarbonylbenzimidazole (154) were formed from 2.37 g of 2-benzyl-5-ethoxycarbonylbenzimidazole and 3.94 g of 2-chlorobenzyl bromide.

[0363] Properties of Compound (153):

¹H-NMR(CDCl₃, δ) : 1.83(3H, t, J=7.1Hz), 4.23(2H, s), 4.35(2H, q, J=7.1Hz), 5.36(2H, s), 6.23(1H, d, J=7.8Hz), 6.97(1H, t, J=7.6Hz), 7.11-7.45(7H, m), 7.85(1H, d, J=8.5Hz), 7.91(1H, s), 8.02(1H, dd, J=1.2 and 8.6Hz).

[0364] Properties of Compound (154):

¹H-NMR(CDCl₃, δ) : 1.41(3H, t, J=7.1Hz), 4.25(2H, s); 4.41(2H, q, J=7.1Hz), 5.33(2H, s), 6.22(1H, d, J=6.9Hz), 6.97(1H, t, J=7.6Hz), 7.12-7.28(7H, m), 7.40(1H, d, J=8.0Hz), 7.95(1H, dd, J=1.6 and 8.6Hz), 8.60(1H, d, J=1.4Hz)

Examples 88 and 89 (Reference examples)

Synthesis of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole (155) and 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole (156)

[0365] In the same manner as in Examples 84 and 85, 0.49 g of 2-benzyl-1-(2,4-dichlorobenzyl)-6-ethoxycarbonylbenzimidazole and 0.52 g of 2-benzyl-1-(2,4-dichlorobenzyl)-5-ethoxycarbonylbenzimidazole (156) were formed from 2.37 g of 2-benzyl-5-ethoxycarbonylbenzimidazole and 4.45 g of 2,4-dichlorobenzyl bromide.

[0366] Properties of Compound (155):

¹H-NMR(CDCl₃, δ) : 1.39(3H, t), 4.24(2H, s), 4.37(2H, q), 5.32(2H, s), 6.08(1H, d, J=8.3Hz), 6.90(1H, d, J=8.4Hz), 7.12-7.24(5H, m), 7.41(1H, s), 7.84(1H, d, J=8.4Hz), 7.88(1H, s), 8.03(1H, d, J=8.4Hz)

[0367] Properties of Compound (156):

¹H-NMR(CDCl₃, δ) : 1.42(3H, t, J=7.1Hz), 4.25(2H, s), 4.41(2H, q, J=7.1Hz), 5.28(2H, s), 6.07(1H, d, J=8.4Hz), 6.90(1H, dd, J=1.9 and 8.4Hz), 7.08-7.28(6H, m), 7.40(1H, d, J=2.1Hz), 7.96(1H, dd, J=1.3 and 8.3Hz), 8.56(1H, d, J=0.9Hz)

Example 90 (Reference example)

Synthesis of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (157)

[0368] Five-percent palladium on carbon (0.50 g) was added to a solution of 4.00 g of ethyl 3-amino-4-nitro-benzoate in 100 ml of methanol, and the mixture was stirred in a hydrogen atmosphere at 50 °C for 16 hours. The solid material was separated through filtration, and the filtrate was concentrated to obtain ethyl 3,4-diaminobenzoate. Twenty milliliters of trifluoroacetic acid were added thereto, and the mixture was stirred at 60 °C for 2 hours. The reaction solution was concentrated, and chloroform was added thereto. The crystals precipitated were separated through filtration, and were dried to give 4.46 g of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (157).

[0369] Properties of Compound (157):

¹H-NMR(DMSO-d₆, δ) : 1.36(3H, t, J=7.0Hz), 4.36(2H, q, J=7.0Hz), 7.82(1H, d, J=8.5Hz), 7.99(1H, dd, J=1.5 and 8.7Hz), 8.33(1H, s)

Examples 91 and 92 (Reference examples)

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Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole (158) and 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (159)

[0370] In the same manner as in Examples 84 and 85, 0.69 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-trifluoromethylbenzimidazole (158) and 0.38 g of 1-(biphenyl-4-ylmethyl)-5-ethoxycarbonyl-2-trifluoromethylbenzimidazole (159) were formed from 2.00 g of 5-ethoxycarbonyl-2-trifluoromethylbenzimidazole and 10.08 g of 4-bromomethylbiphenyl.

[0371] Properties of Compound (158):

¹H-NMR(CDCl₃, δ) : 1.39(3H, t), 4.38(2H, q), 5.64(2H, s), 7.18(2H, d, J=8.2Hz), 7.34(1H, t, J=7.4Hz), 7.42(2H, t, J=7.4Hz), 7.52-7.57(4H, m), 7.95(1H, d, J=8.8Hz), 8.09(2H, dd, J=1.4 and 8.8Hz), 8.14(1H, d, J=1.1Hz)

[0372] Properties of Compound (159):

¹H-NMR(CDCl₃, δ) : 1.40(3H, t), 4.40(2H, q), 5.59(2H, s), 7.16(2H, d, J=8.1Hz), 7.34(2H, t, J=6.2Hz), 7.41(2H, t, J=7.5Hz), 7.53(4H, m), 8.08(1H, dd, J=1.3 and 9.1Hz), 8.65(1H, s)

Production Example 38

Production of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole

[0373] A solution of 2.66 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole in 20 ml of tetrahydrofuran was slowly added to a solution of 1.54 g of lithium aluminum hydride in 20 ml of tetrahydrofuran at a temperature of from 20 to 25°C. Further, the mixture was stirred at room temperature for 1 hour. Thirty milliliters of tetrahydrofuran were added thereto to dilute the reaction solution. Lithium ammonium hydride was decomposed and solidified with a saturated aqueous solution of sodium sulfate, and the tetrahydrofuran layer was separated. The solvent was distilled off, and the residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1) to give 1.45 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole.

[0374] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 2.53(3H, s), 4.77(2H, s), 5.39(2H, s), 6.40(1H, d, J=7.7Hz), 7.08(1H, t, J=7.7Hz), 7.20-7.28(3H, m), 7.45(1H, d, J=7.9Hz), 7.70(1H, d, J=8.2Hz)

Production Example 39

Production of 1-(biphenyl-4-ylmethyl)-6-hydroxymethyl-2-methylbenzimidazole

[0375] In the same manner as in Production Example 38, 3.72 g of 1-(biphenyl-4-ylmethyl)-6-hydroxymethyl-2-methylbenzimidazole were formed from 5.30 g of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 2.17 g of lithium aluminum hydride.

[0376] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 2.59(3H, s), 4.78(2H, s), 5.37(2H, s), 7.11(2H, d, J=8.3Hz), 7.24(1H, d, J=8.3Hz), 7.30-7.37(2H, m), 7.42(2H, t), 7.51-7.56(4H, m), 7.70(1H, d, J=8.2Hz).

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Production Example 40

Production of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride

[0377] Five milliliters of thionyl chloride were added to 3.56 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole, and the mixture was stirred at room temperature for 20 minutes and then at 80°C for 20 minutes. After excess thionyl chloride was distilled off under reduced pressure, the residue was dissolved in 10 ml of chloroform, and the solution was crystallized from hexane. The crystals were separated through filtration, washed with hexane, and

dried to give 4.07 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride.

[0378] Properties of the compound:

⁵ ¹H-NMR(CDCl₃, δ) : 3.01(3H, s), 4.68(2H, s), 5.61(2H, s), 6.71(1H, d, J=7.5Hz), 7.24-7.29(1H, m), 7.38(1H, t, J=7.7Hz), 7.44(1H, s), 7.52(2H, d, J=8.2Hz), 7.92(1H, d, J=8.4Hz).

Production Example 41

Production of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole

¹⁰ [0379] Two milliliters of thionyl chloride were added to a solution of 3.62 g of 1-(biphenyl-4-ylmethyl)-6-hydroxymethyl-2-methylbenzimidazole in 30 ml of chloroform at room temperature, and the mixture was stirred at 60 °C for 1 hour. A sodium hydrogencarbonate aqueous solution was added thereto to stop the reaction. The chloroform layer was washed with water, and was dried. The solvent was distilled off under reduced pressure, and the residue was crystallized from ethyl acetate. The crystals were separated through filtration, washed with ethyl acetate, and then dried to give 2.04 g of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole.

¹⁵ [0380] Properties of the compound:

²⁰ ¹H-NMR(CDCl₃, δ) : 2.67(3H, s), 4.71(2H, s), 5.40(2H, s), 7.12(2H, d, J=8.2Hz), 7.31-7.38(3H, m), 7.43(2H, t), 7.52-7.58(4H, m), 7.75(1H, d, J=8.2Hz).

Production example 42

Production of 1-(2-chlorobenzyl)-6-formyl-2-methylbenzimidazole

²⁵ [0381] Manganese dioxide (3.46 g) was added to a solution of 3.46 g of 1-(2-chlorobenzyl)-6-hydroxymethyl-2-methylbenzimidazole in 100 ml of toluene, and the toluene was heat-refluxed for 3.5 hours while the mixture was dehydrated using a molecular sieve 4Å. The solid material was separated through filtration, and was washed with chloroform. The filtrate was concentrated to give 3.35 g of 1-(2-chlorobenzyl)-6-formyl-2-methylbenzimidazole.

³⁰ [0382] Properties of the compound:

³⁵ ¹H-NMR(CDCl₃, δ) : 2.61(3H, s), 5.48(2H, s), 6.42(1H, d, J=7.8Hz), 7.11(1H, t, J=7.6Hz), 7.27(1H, t), 7.48(1H, d, J=8.0Hz), 7.76(1H, s), 7.81(1H, dd, J=1.4 and 8.3Hz), 7.86(1H, d, J=8.3Hz), 10.02(1H, s). IR(KBr) : 1676cm⁻¹. mp : 124.1-125.2°C

Production Example 43

Production of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetonitrile

⁴⁰ [0383] Potassium cyanate (0.450 g) and 0.450 g of 18-crown-6 were added to a solution of 1.20 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole in 10 ml of dimethylsulfoxide, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was extracted with the addition of chloroform, water and a small amount of aqueous ammonia. The organic layer was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 20:1) to give 0.500 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetonitrile.

⁴⁵ [0384] Properties of the compound:

⁵⁰ ¹H-NMR(CDCl₃, δ) : 2.52(3H, s), 3.80(2H, s), 5.37(2H, s), 6.40(1H, d, J=7.6Hz), 7.09(1H, t), 7.10-7.19(2H, m), 7.23(1H, t), 7.44(1H, d, J=7.9Hz), 7.70(1H, d, J=8.2Hz).

Production Example 44

Production of 6-carboxy-1-(2-chlorobenzyl)benzimidazole

⁵⁵ [0385] To 0.490 g of 4-amino-3-(2-chlorobenzyl)aminobenzoic acid formed by the method described in U. S. Patent No. 5,294,631 were added 0.5 ml of 98% formic acid, and the mixture was refluxed for 1 hour. The solid material precipitated was collected, washed with water, and dried to give 0.468 g of 6-carboxy-1-(2-chlorobenzyl)benzimidazole.

[0386] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 5.69(2H, s), 7.02(1H, dd, J=1.5 and 7.7Hz), 7.30(1H, t, J=7.5Hz), 7.36(1H, dt, J=1.7 and 7.5Hz), 7.53(1H, dd, J=1.3 and 7.9Hz), 7.75(1H, d, J=8.4Hz), 7.83(1H, dd, J=1.5 and 8.4Hz), 8.09(1H, s), 8.54(1H, s), 12.8(1H, br s)

5 Example 93 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92)

[0387] One-hundred grams of 2-chlorobenzyl bromide were added to a solution of 86.0 g of ethyl 4-acetylaminobenzoate and 37.3 g of potassium carbonate in 750 ml of ethanol, and the mixture was stirred at 60°C for 14 hours. The solid material was separated through filtration, and the filtrate was concentrated to 500 ml under reduced pressure. Then, 38.7 g of 35 % hydrochloric acid were added thereto, and the mixture was stirred at 60°C for 2 hours. The solid material was separated through filtration, and the residue was neutralized with sodium hydrogencarbonate. Ethanol was distilled off under reduced pressure. The residue was extracted three times with ethyl acetate and with water. The organic layer was washed with water, and was dried. The solvent was distilled off until the amount of the organic layer reached 300 ml. The crystals precipitated were separated through filtration, and were recrystallized from ethanol to obtain 54.3 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92). The filtrate was also all collected, and was concentrated. The resulting crystals were recrystallized from ethanol to give 18.1 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (92).

[0388] Properties of Compound (92):

¹H-NMR(CDCl₃, δ) : 1.39(3H, t, J=7.1Hz), 2.57(3H, s), 4.37(2H, q, J=7.1Hz), 5.46(2H, s), 6.41(1H, d, J=7.8Hz), 7.10(1H, t, J=7.8Hz), 7.25(1H, t), 7.47(1H, d, J=8.0Hz), 7.75(1H, d, J=8.4Hz), 7.94(1H, s), 8.00(1H, dd, J=1.5 and 8.4Hz)

mp : 126.0-127.0°C.

Example 94 (Reference example)

Synthesis of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121)

[0389] To 60.0 g of 1-(2-chlorobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole were added 240 g of a 10% sodium hydroxide aqueous solution and 200 ml of ethanol, and the mixture was heat-refluxed for 2 hours. The reaction solution was cooled, and was then adjusted to a pH of 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 54.7 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole (121).

[0390] Properties of Compound (121):

¹H-NMR(DMSO-d₆, δ) : 2.51(3H, s), 5.62(2H, s), 6.54(1H, d, J=7.7Hz), 7.23(1H, t, J=7.5Hz), 7.33(1H, t, J=7.7Hz), 7.55(1H, d, J=8.0Hz), 7.63(1H, d, J=8.4Hz), 7.79(1H, d, J=8.4Hz), 7.95(1H, B).
mp : 300.8-303.0°C

Example 95 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid (160)

[0391] To 0.500 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetonitrile was added 10% hydrochloric acid, and the mixture was heat-refluxed for 15 hours. The reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, and was extracted with chloroform. The organic layer was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1 to 4:1) to give 0.170 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid (160).

[0392] Properties of Compound (160):

¹H-NMR(CDCl₃, δ) : 2.42(3H, s), 3.56(2H, s), 5.15(2H, s), 6.33(1H, d), 6.96(1H, t), 7.03(1H, s), 7.13(2H, m), 7.35(1H, d, J=7.9Hz), 7.62(1H, d), 8.90(1H, br s)

Example 96 (Reference example)

Synthesis of methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate

- 5 [0393] Methyl trifluorophosphoranicacetate (4.49 g) was added to a solution of 2.73 g of 1-(2-chlorobenzyl)-6-formyl-
2-methylbenzimidazole in 50 ml of 1,4-dioxane, and the mixture was stirred for 6 hours while being heat-refluxed. After
the reaction solution was cooled, the solvent was distilled off under reduced pressure, and the residue was purified
through silica-gel chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1) to obtain 7.43 g of
crude methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate (161). This crude product was used in the subse-
10 quent reaction at once.

Example 97 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid

- 15 [0394] The above-mentioned crude methyl 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylate (3.29 g) was dis-
solved in 20 ml of ethanol, and 10.1 g of a 5% sodium hydroxide aqueous solution were added thereto. The mixture
was refluxed for 2 hours. The reaction solution was neutralized with a hydrochloric acid aqueous solution. The solvent
was distilled off under reduced pressure, and the residue was purified through silica-gel chromatography (eluent: a
20 mixture of chloroform and methanol at a ratio of from 9:1 to 6:1) to give 1.10 g of 1-(2-chlorobenzyl)-2-methylbenzim-
idazole-6-acrylic acid.

[0395] Properties of Compound (162):

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.56(3\text{H}, \text{s}), 5.65(2\text{H}, \text{s}), 6.54(1\text{H}, \text{d}, J=15.9\text{Hz}), 6.62(1\text{H}, \text{d}, J=7.6\text{Hz}), 7.25(1\text{H}, \text{t}), 7.35$
(1H, t), 7.56(1H, d, J=8.1Hz), 7.60-7.70(3H, m), 7.99(1H, s), 12.35(1H, br s)

Example 98

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

- 30 [0396] N,N'-carbonyldiimidazole (45.8 g) was added at a time to a solution of 45.0 g of 6-carboxy-1-(2-chlorobenzyl)-
2-methylbenzimidazole in 950 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1
hour. Subsequently, 47.1 g of benzenesulfonamide and 35.0 g of diazabicycloundecene were added thereto, and the
mixture was stirred at 100°C for 70 hours. The reaction solution was cooled, and the solvent was distilled off under
35 reduced pressure. To the residue were added 300 ml of water and 200 ml of methanol. Further, 60.7 g of 35% hydro-
chloric acid were added thereto to adjust the solution to a pH of 5.5. The crystals precipitated were separated through
filtration, washed with 200 ml of a mixed solution of methanol and water (at a ratio of 1:1), and dried to obtain 38.4 g
of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole. Water was added to the filtrate. The crys-
tals precipitated were separated through filtration, washed with water, and dried. The amount of the crystals was 13.3
40 g. The crystals were combined, and were dissolved by being heated with the addition of 3300 ml of acetone and 900
ml of water. From this solution, 200 ml of the solvent were distilled off while being heated, and the residue was cooled.
The crystals precipitated were separated through filtration, and were dried to give 33.8 g of 6-benzenesulfonylcar-
bamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

[0397] Properties of Compound (163):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.53(3\text{H}, \text{s}), 5.46(2\text{H}, \text{s}), 6.34(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.11(1\text{H}, \text{m}), 7.27(1\text{H}, \text{m}), 7.48(1\text{H}, \text{m}),$
7.52(2H, m), 7.60(1H, m), 7.69(1H, d, J=8.6Hz), 7.90(1H, m), 8.09(2H, m), 8.11(1H, s), 11.84(1H, br s).
IR(KBr) : 1684, 1448cm⁻¹.
Mass(FAB) : m/e 440(M+1).
50 mp : 273.5-274.3°C.

Example 99

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole (164)

- 55 [0398] In the same manner as in Example 98, 0.473 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-
2-ethylbenzimidazole (164) were formed from 0.600 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-carboxybenzimidazole,
0.546 g of N,N'-carbonyldiimidazole, 0.529 g of benzenesulfonamide and 0.512 g of diazabicycloundecene.

[0399] Properties of Compound (164):

⁵ ¹H-NMR(DMSO-d₆, δ) : 1.29(3H, t, J=7.4Hz), 2.88(2H, q, J=7.4Hz), 5.59(2H, s), 7.16(2H, d, J=8.2Bz), 7.33-7.37
1H, m), 7.44(2H, t, J=7.5Hz), 7.59-7.71(8H, m), 7.74(1H, dd, J=8.4 and 1.4Hz), 7.98-8.02(2H, m), 8.21(1H, s),
12.43(1H, s).
IR(KBr) : 1684cm⁻¹.
mp : 149.5-157.0°C

Example 100

¹⁰ Synthesis of 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (165)

[0400] In the same manner as in Example 98, 0.480 g of 5-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (165) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.470 g of benzenesulfonamide and 0.456 g of diazabicycloundecene.

[0401] Properties of Compound (165):

²⁰ ¹H-NMR(DMSO-d₆, δ) : 2.53(3H, s), 5.61(2H, s), 6.57(1H, d, J=7.4Hz), 7.22(1H, t), 7.33(1H, t), 7.50(1H, d,
J=8.6Hz), 7.54(1H, dd, J=7.9 and 0.9Hz), 7.63(2H, t), 7.71(2H, m), 8.00(2H, d, J=7.3Hz), 8.21(1H, d, J=1.4Hz),
12.50(1H, br s).
IR(KBr) : 1685cm⁻¹.
mp : 137.0-138.5°C.

Example 101

²⁵ Synthesis of 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (166)

[0402] In the same manner as in Example 98, 0.520 g of 5-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (166) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.573 g of 4-chlorobenzenesulfonamide and 0.456 g of diazabicycloundecene.

[0403] Properties of Compound (166):

³⁵ ¹H-NMR(DMSO-d₆, δ) : 2.49(3H, s), 5.58(2H, s), 6.51(1H, d, J=7.6Hz), 7.21(1H, t), 7.32(1H, t), 7.45(1H, d,
J=8.6Hz), 7.53(1H, d, J=7.8Hz), 7.69(3H, d, J=8.6Hz), 7.99(2H, d, J=8.6Hz), 8.18(1H, s), 12.58(1H, br s).
IR(KBr) : 1619cm⁻¹.
mp : 261.5-263.0°C

Example 102

⁴⁰ Synthesis of 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)benzimidazole (167)

[0404] In the same manner as in Example 98, 0.352 g of 1-(2-chlorobenzyl)-2-methyl-5-(2-naphthalenesulfonylcarbamoyl)-benzimidazole (167) were formed from 0.450 g of 5-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.620 g of 2-naphthalenesulfonamide and 0.456 g of diazabicycloundecene.

[0405] Properties of Compound (167):

⁵⁰ ¹H-NMR(DMSO-d₆, δ) : 2.48(3H, s), 5.56(2H, s), 6.49(1H, d, J=7.7Hz), 7.20(1H, t, J=7.6Hz), 7.31(1H, t, J=7.7Hz),
7.44(1H, d, J=8.6Hz), 7.52(1H, d, J=8.0Hz), 7.66-7.75(3H, m), 7.97(1H, d, J=8.8Hz), 8.04(1H, d, J=8.0Hz), 8.14
(1H, d, J=8.8Hz), 8.19(1H, s), 8.23(1H, d, J=8.0Hz), 8.68(1H, s), 12.55(1H, br s).
IR(KBr) : 1685cm⁻¹.
mp : 236.5-238.0°C

Example 103

⁵⁵ Synthesis of 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole (168)

[0406] In the same manner as in Example 98, 0.564 g of 1-(2-chlorobenzyl)-6-methanesulfonylcarbamoyl-2-methylbenzimidazole (168) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of

N,N'-carbonyldiimidazole, 0.316 g of methanesulfonamide and 0.506 g of diazabicycloundecene.

[0407] Properties of Compound (168):

⁵ ¹H-NMR(DMSO-d₆, δ) : 2.49(3H, s), 3.35(3H, s), 5.60(2H, s), 6.43(1H, d, J=7.8Hz), 7.23(1H, t), 7.34(1H, t, J=7.7Hz), 7.57(1H, d, J=8.0Hz), 7.68(1H, d, J=8.5Hz), 7.81(1H, dd, J=1.7 and 8.5Hz), 8.13(1H, d, J=1.5Hz), 11.94(1H, br s).
IR(KBr) : 1670cm⁻¹.
mp : 302.0-303.0°C

¹⁰ Example 104

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (169)

[0408] In the same manner as in Example 98, 0.595 g of 6-(1-butanesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (169) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of N,N'-carbonyldiimidazole, 0.456 g of 1-butanesulfonamide and 0.506 g of diazabicycloundecene.

[0409] Properties of Compound (169):

²⁰ ¹H-NMR(DMSO-d₆, δ) : 0.84(3H, t, J=7.4Hz), 1.38(2H, m), 1.65(2H, m), 2.49(3H, s), 3.49(2H, m), 5.60(2H, s), 6.44(1H, d, J=7.6Hz), 7.23(1H, t, J=7.6Hz), 7.35(1H, t), 7.56(1H, d, J=8.0Hz), 7.68(1H, d, J=8.4Hz), 7.80(1H, dd, J=1.6 and 8.4Hz), 8.11(1H, d, J=1.4Hz), 11.86(1H, br s).
IR(KBr) : 1684cm⁻¹.
mp : 214.0-217.0°C

²⁵ Example 105

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)benzimidazole (170)

[0410] In the same manner as in Example 98, 0.309 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-octanesulfonylcarbamoyl)-benzimidazole (170) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.406 g of 1-octanesulfonamide and 0.404 g of diazabicycloundecene.

[0411] Properties of Compound (170):

³⁵ ¹H-NMR(DMSO-d₆, δ) : 0.82(3H, t, J=7.3Hz), 1.13-1.28(8H, m), 1.32-1.41(2H, m), 1.62-1.71(2H, m), 2.50(3H, s), 3.50(2H, t, J=8.5Hz), 5.61(2H, s), 6.45(1H, d, J=7.7Hz), 7.24(1H, t, J=7.5Hz), 7.35(1H, t, J=7.5Hz), 7.58(1H, d, J=8.0Hz), 7.69(1H, d, J=8.4Hz), 7.81(1H, d, J=8.5Hz), 8.12(1H, s), 11.86(1H, s).
IR(KBr) : 1674cm⁻¹.
mp : 180.0-183.0°C

⁴⁰ Example 106

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(2-propanesulfonylcarbamoyl)benzimidazole (171)

[0412] In the same manner as in Example 98, 0.417 g of 1-(2-chlorobenzyl)-2-methyl-6-(2-propanesulfonylcarbamoyl)-benzimidazole (171) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.328 g of 2-propanesulfonamide and 0.404 g of diazabicycloundecene.

[0413] Properties of Compound (171):

⁵⁰ ¹H-NMR(DMSO-d₆, δ) : 1.30(6H, d, J=6.9Hz), 2.50(3H, s), 3.81-3.87(1H, m), 5.62(2H, s), 6.46(1H, d, J=7.7Hz), 7.25(1H, t, J=7.5Hz), 7.35(1H, t, J=7.5Hz), 7.62(1H, d, J=7.9Hz), 7.69(1H, d, J=8.5Hz), 7.81(1H, d, J=8.6Hz), 8.12(1H, s), 11.83(1H, s).
IR(KBr) : 1670cm⁻¹.
mp : 215.0-217.5°C.

Example 107

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (172)

5 [0414] In the same manner as in Example 98, 0.349 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (172) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.273 g of 1-butanesulfonamide and 0.303 g of diazabicycloundecene.

[0415] Properties of Compound (172):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.85(3H, t, $J=7.4\text{Hz}$), 1.36-1.43(2H, m), 1.63-1.72(2H, m), 2.57(3H, s), 3.52(2H, t, $J=7.7\text{Hz}$), 5.60(2H, s), 7.21(2H, d, $J=8.2\text{Hz}$), 7.35(1H, t, $J=7.3\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.60-7.68(5H, m), 7.81(1H, dd, $J=1.6$ and 8.4Hz), 8.26(1H, d, $J=1.4\text{Hz}$), 11.97(1H, s).
 IR(KBr) : 1676cm $^{-1}$.
 mp : 219.5-222.5°C

15

Example 108

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (173)

20 [0416] In the same manner as in Example 98, 0.459 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (173) were formed from 0.400 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.364 g of 1-butanesulfonamide and 0.404 g of diazabicycloundecene.

[0417] Properties of Compound (173):

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.85(3H, t, $J=7.3\text{Hz}$), 1.36-1.42(2H, m), 1.63-1.70(2H, m), 2.50(3H, s), 3.51(2H, t, $J=7.7\text{Hz}$), 5.59(2H, s), 6.45(1H, d, $J=8.4\text{Hz}$), 7.33(1H, dd, $J=2.1$ and 8.4Hz), 7.69(1H, d, $J=8.4\text{Hz}$), 7.76(1H, d, $J=2.0\text{Hz}$), 7.81(1H, dd, $J=1.7$ and 8.5Hz), 8.11(1H, d, $J=1.3\text{Hz}$), 11.90(1H, s).
 IR(KBr) : 1670cm $^{-1}$.
 mp : 222.0-223.0°C

30

Example 109

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (174)

35 [0418] In the same manner as in Example 98, 0.300 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (174) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.340 g of N,N'-carbonyldiimidazole, 0.300 g of butanesulfonamide and 0.320 g of diazabicycloundecene.

[0419] Properties of Compound (174):

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.85(3H, t, $J=7.3\text{Hz}$), 1.30(3H, t, $J=7.5\text{Hz}$), 1.35-1.44(2H, m), 1.64-1.72(2H, m), 2.90(2H, q, $J=7.4\text{Hz}$), 3.52(2H, t, $J=7.7\text{Hz}$), 5.61(2H, s), 7.19(2H, d, $J=8.3\text{Hz}$), 7.35(1H, t, $J=7.3\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.61-7.67(4H, m), 7.71(1H, d, $J=8.5\text{Hz}$), 7.82(1H, dd, $J=1.6$ and 8.5Hz), 8.27(1H, d, $J=1.3\text{Hz}$), 12.01(1H, s).IR (Nujol) : 1687, 1682cm $^{-1}$.
 mp : 171.8-173.0°C

45

Example 110

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (175)

50 [0420] In the same manner as in Example 98, 0.508 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (175) were formed from 0.483 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-trifluoromethylbenzimidazole, 0.396 g of N,N'-carbonyldiimidazole, 0.383 g of benzenesulfonamide and 0.371 g of diazabicycloundecene.

[0421] Properties of Compound (175):

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 5.81(2H, s), 7.15(2H, d, $J=8.3\text{Hz}$), 7.35(1H, t, $J=7.5\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.60-7.66(6H, m), 7.70(1H, t, $J=7.4\text{Hz}$), 7.91(1H, dd, $J=8.7$ and 1.4Hz), 7.96-8.01(3H, m), 8.42(1H, s), 12.65(1H, s).
 IR(KBr) : 1685cm $^{-1}$.
 mp : 164.5-167.0°C

Example 111

Synthesis of 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (176)

- 5 [0422] In the same manner as in Example 98, 0.286 g of 5-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-trifluoromethylbenzimidazole (176) were formed from 0.270 g of 1-(biphenyl-4-ylmethyl)-5-carboxy-2-trifluoromethylbenzimidazole, 0.221 g of N,N'-carbonyldiimidazole, 0.214 g of benzenesulfonamide and 0.207 g of diazabicycloundecene.
- [0423] Properties of Compound (176):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 5.79(2H, s), 7.15(2H, d, $J=8.1\text{Hz}$), 7.35(1H, t, $J=7.5\text{Hz}$), 7.43(2H, t, $J=7.5\text{Hz}$), 7.59-7.67
(6H, m), 7.72(1H, t, $J=7.6\text{Hz}$), 7.83(1H, d, $J=8.8\text{Hz}$), 7.94(1H, d, $J=8.9\text{Hz}$), 8.02(2H, d, $J=7.4\text{Hz}$), 8.49(1H, s), 12.69
(1H, s).
IR(KBr) : 1699cm $^{-1}$
mp : 248.5-251.0°C

Example 112

Synthesis of 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (177)

- 20 [0424] In the same manner as in Example 98, 0.730 g of 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)-benzimidazole (177) were formed from 0.930 g of 6-carboxy-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole, 0.972 g of N,N'-carbonyldiimidazole, 0.942 g of benzenesulfonamide and 0.906 g of diazabicycloundecene.
- [0425] Properties of Compound (177):

25 $^1\text{H-NMR}$ (DMSO-d₆, δ) : 1.04 (4H, m), 2.15 (1H, m), 5.70 (2H, s), 6.85 (1H, t, $J=7.5\text{Hz}$), 7.12 (1H, t, $J=7.5\text{Hz}$),
7.22-7.38 (2H, m), 7.54-7.70 (5H, m), 7.99 (2H, d, $J=7.5\text{Hz}$), 8.11 (1H, s) white powder.

Example 113

- 30 Synthesis of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acrylamide (178)

[0426] In the same manner as in Example 98, 1.05 g of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acrylamide (178) were formed from 1.10 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylic acid, 1.09 g of N,N'-carbonyldiimidazole, 1.06 g of benzenesulfonamide and 1.02 g of diazabicycloundecene.

- 35 [0427] Properties of Compound (178):

1H-NMR(DMSO-d₆, δ) : 2.47(3H, s), 5.55(2H, s), 6.46-6.55(2H, m), 7.22(1H, t, $J=7.6\text{Hz}$), 7.32(1H, t, $J=7.7\text{Hz}$),
7.40(1H, d, $J=8.4\text{Hz}$), 7.52-7.66(6H, m), 7.69(1H, t), 7.93(2H, d, $J=7.9\text{Hz}$), 12.17(1H, br s).
IR(KBr) : 1687cm $^{-1}$.
Mass(FAB) : m/e 466(M+1).
mp : 243.1-244.3°C

Example 114

- 45 Synthesis of N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide (179)

[0428] In the same manner as in Example 98, 0.09 g of N-benzenesulfonyl-2-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]acetamide (179) were formed from 0.170 g of 1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acetic acid, 0.175 g of N,N'-carbonyldiimidazole, 0.170 g of benzenesulfonamide and 0.164 g of diazabicycloundecene.

- 50 [0429] Properties of Compound (179):

1H-NMR(DMSO-d₆, δ) : 2.44(3H, s), 3.57(2H, s), 5.46(2H, s), 6.41(1H, d, $J=7.7\text{Hz}$), 6.96(1H, d, $J=7.0\text{Hz}$), 7.16
(1H, s), 7.20(1H, t), 7.32(1H, t), 7.47(1H, d, $J=8.2\text{Hz}$), 7.52-7.59(3H, m), 7.67(1H, t, $J=7.5\text{Hz}$), 7.84(2H, d, $J=7.4\text{Hz}$),
12.28(1H, br s).
IR(KBr) 1719cm $^{-1}$.
mp : 236.2-237.8°C

Example 115 (Reference example)

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180)

- 5 [0430] Dichloromethane (150 ml) and some drops of N,N-dimethylformamide were added to 9.00 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, and the mixture was cooled with ice. Oxalyl chloride (6.84 g) were added dropwise thereto, and the mixed solution was stirred for some minutes. Further, this solution was stirred at room temperature for 1.5 hours, and was then concentrated to a volume of approximately 1/3 of the original volume under reduced pressure. The solid material precipitated was collected, and was added to a solution of 2.69 g of 2-aminomethylpyridine and 7.34 g of triethylamine in 200 ml of dichloromethane in some divided portions. After the mixture was stirred for 15 hours, the reaction solution was washed three times with water and then with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was concentrated under reduced pressure, and was crystallized from ethyl acetate. The crystals were separated through filtration, and were dried to give 4.35 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180).
- 10 [0431] Properties of Compound (180):

¹H-NMR(CDCl₃, δ) : 2.56(3H, s), 4.76(2H, d, J=4.8Hz), 5.40(2H, s), 6.33(1H, d, J=8.4Hz), 7.07(1H, dd, J=8.4 and 2.0Hz), 7.22(1H, dd, J=7.4 and 4.9Hz), 7.33(1H, d, J=7.9Hz), 7.48(1H, d, J=2.1Hz), 7.62-7.79(4H, m), 7.86(1H, d, J=1.1Hz), 8.57= (1H, d, J=4.9Hz).

20 IR(KBr) : 1645cm⁻¹

mp : 204.5-206.5°C

Example 116 (Reference example)

Synthesis of 1-methyl-2-n-propyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (181)

- 25 [0432] In the same manner as in Example 115, 0.213 g of 1-methyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (181) were formed from 0.402 g of 6-carboxy-1-methyl-2-n-propylbenzimidazole, 0.468 g of oxalyl chloride, 0.199 g of 2-aminomethylpyridine and 0.559 g of triethylamine.

- 30 [0433] Properties of Compound (181):

¹H-NMR(CDCl₃, δ) : 1.08(3H, t, J=7.4Hz), 1.92(2H, m), 2.88(2H, m), 3.76(3H, s), 4.80(2H, d, J=4.8Hz), 7.22(1H, dd, J=2.5 and 7.5Hz), 7.35(1H, d, J=7.8Hz), 7.67-7.77(4H, m), 7.80(1H, s), 8.58(1H, dd, J=4.9 and 0.9Hz).

IR(KBr) : 1647cm⁻¹.

35 mp : 140.5-141.5°C

Example 117 (Reference example)

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (182)

- 40 [0434] In the same manner as in Example 115, 0.164 g of 1-(2-chlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (182) were formed from 0.300 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.253 g of oxalyl chloride, 0.108 g of 2-aminomethylpyridine and 0.302 g of triethylamine.

- 45 [0435] Properties of Compound (182):

¹H-NMR(CDCl₃, δ) : 2.56(3H, s), 4.76(2H, d, J=4.8Hz), 5.45(2H, s), 6.40(1H, d, J=7.8Hz), 7.08(1H, t, J=7.6Hz), 7.20-7.27(2H, m), 7.33(1H, d, J=7.8Hz), 7.45(1H, dd, J=0.9 and 8.1Hz), 7.64(1H, s), 7.65-7.69(1H, m), 7.72(1H, dd, J=1.5 and 8.4Hz), 7.77(1H, d, J=8.4Hz), 7.88(1H, d, J=1.2Hz), 8.56(1H, d, J=4.7Hz).

IR(KBr) : 1646cm⁻¹.

50 mp : 156.5-157.5°C

Example 118 (Reference example)

Synthesis of 2-n-propyl-1-i-propyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (183)

- 55 [0436] In the same manner as in Example 115, 0.020 g of 2-n-propyl-1-i-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (183) were formed from 0.095 g of 6-carboxy-2-n-propyl-1-i-propylbenzimidazole, 0.100 g of oxalyl chloride, 0.039 g of 2-aminomethylpyridine and 0.097 g of triethylamine.

[0437] Properties of Compound (183):

⁵ ¹H-NMR(CDCl₃, δ) : 1.08(3H, t, J=7.4Hz), 1.69(6H, d, J=7.1Hz), 1.87-1.93(2H, m), 2.90(2H, t, J=7.8Hz), 4.69-4.75(1H, m), 4.80(2H, d, J=4.9Hz), 7.23(1H, dd, J=7.3 and 2.1Hz), 7.37(1H, d, J=7.7Hz), 7.62-7.77(4H, m), 8.21(1H, s), 8.58(1H, d, J=4.5Hz).

IR(KBr) : 1631cm⁻¹.

mp : 155.0-156.9°C

Example 119 (Reference example)

¹⁰ Synthesis of 1-n-butyl-2-n-propyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (184)

[0438] In the same manner as in Example 115, 0.283 g of 1-n-butyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (184) were formed from 0.500 g of 1-n-butyl-6-carboxy-2-n-propylbenzimidazole, 0.487 g of oxalyl chloride, 0.208 g of 2-aminomethylpyridine and 0.582 g of triethylamine.

[0439] Properties of Compound (184):

¹⁵ ¹H-NMR(CDCl₃, δ) : 0.97(3H, t, J=7.3Hz), 1.08(3H, t, J=7.4Hz), 1.37-1.46(2H, m), 1.76-1.83(2H, m), 1.92-2.00(2H, m), 2.86(2H, t, J=7.8Hz), 4.15(2H, t, J=7.6Hz), 4.81(2H, d, J=4.8Hz), 7.23(1H, dd, J=7.3 and 2.4Hz), 7.36(1H, d, J=7.8Hz), 7.63-7.76(4H, m), 8.02(1H, s), 8.58(1H, d, J=4.7Hz).

IR(KBr) : 1631cm⁻¹.

mp : 105.8-107.2°C

Example 120 (Reference example)

²⁵ Synthesis of 1-(3-chlorobenzyl)-2-n-propyl-6-[2-pyridylmethyl]-carbamoyl]benzimidazole (185)

[0440] In the same manner as in Example 115, 0.311 g of 1-(3-chlorobenzyl)-2-n-propyl-6-[2-pyridylmethyl]carbamoyl]benzimidazole (185) were formed from 0.580 g of 6-carboxy-1-(3-chlorobenzyl)-2-n-propylbenzimidazole, 0.407 g of oxalyl chloride, 0.173 g of 2-aminomethylpyridine and 0.486 g of triethylamine.

[0441] Properties of Compound (185):

³⁰ ¹H-NMR(CDCl₃, δ) : 1.03(3H, t, J=7.4Hz), 1.85-1.93(2H, m), 2.80(2H, t, J=7.5Hz), 4.77(2H, d, J=4.8Hz), 5.36(2H, s), 6.86(1H, d, J=7.4Hz), 7.02(1H, s), 7.20-7.28(3H, m), 7.33(1H, d, J=7.8Hz), 7.63-7.73(3H, m), 7.79(1H, d, J=8.4Hz), 7.91(1H, d, J=1.3Hz), 8.57(1H, d, J=4.7Hz).

IR(KBr) : 1643cm⁻¹.

mp : 157.7-158.8°C

Example 121 (Reference example)

⁴⁰ Synthesis of 1-benzyl-2-n-propyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole (186)

[0442] In the same manner as in Example 115, 0.350 g of 1-benzyl-2-n-propyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (186) were formed from 0.850 g of 1-benzyl-6-carboxy-2-n-propylbenzimidazole, 0.949 g of oxalyl chloride, 0.404 g of 2-aminomethylpyridine and 1.132 g of triethylamine.

[0443] Properties of Compound (186):

⁴⁵ ¹H-NMR(CDCl₃, δ) : 1.01(3H, t, J=7.4Hz), 1.83-1.92(2H, m), 2.82(2H, t, J=7.6Hz), 4.77(2H, d, J=4.8Hz), 5.40(2H, s), 7.03(2H, d, J=6.5Hz), 7.21(1H, dd, J=7.1 and 2.1Hz), 7.18-7.34(4H, m), 7.60(1H, s), 7.65-7.72(2H, m), 7.78(1H, d, J=8.4Hz), 7.94(1H, d, J=1.2Hz), 8.56(1H, d, J=4.2Hz).

IR(KBr) : 1642cm⁻¹.

mp : 121.9-123.1°C

Example 122 (Reference example)

⁵⁵ Synthesis of 1-(4-chlorobenzyl)-2-propyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (187)

[0444] In the same manner as in Example 115, 0.089 g of 1-(4-chlorobenzyl)-2-propyl-6-[(2-pyridylmethyl)car-

bamoyl]-benzimidazole (187) were formed from 0.547 g of 6-carboxy-1-(4-chlorobenzyl)-2-propylbenzimidazole, 0.384 g of oxalyl chloride, 0.163 g of 2-aminomethylpyridine and 0.458 g of triethylamine.

[0445] Properties of Compound (187):

5 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 1.02(3H, t, $J=7.4\text{Hz}$), 1.84-1.92(2H, m), 2.77-2.83(2H, m), 4.76(2H, d, $J=4.8\text{Hz}$), 5.36(2H, s),
 6.96(2H, d, $J=8.3\text{Hz}$), 7.22(1H, dd, $J=6.4$ and 0.4Hz), 7.27(2H, dd, $J=8.3$ and 1.3Hz), 7.33(1H, d, $J=7.8\text{Hz}$),
 7.62-7.73(3H, m), 7.78(1H, d, $J=8.4\text{Hz}$), 7.91(1H, d, $J=0.9\text{Hz}$), 8.56(1H, dd, $J=4.9$ and 0.8Hz).
 IR(KBr) : 1643cm^{-1} .
 mp : 158.8 - 161.0°C

10

Example 123 (Reference example)

Synthesis of 2-benzyl-1-nethyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (188)

15 **[0446]** In the same manner as in Example 115, 0.171 g of 2-benzyl-1-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (188) were formed from 0.310 g of 2-benzyl-6-carboxy-1-methylbenzimidazole, 0.295 g of oxalyl chloride, 0.108 g of 2-aminomethylpyridine and 0.303 g of triethylamine.

[0447] Properties of Compound (188):

20 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 3.66(3H, s), 4.35(2H, s), 4.80(2H, d, $J=4.8\text{Hz}$), 7.21-7.37(7H, m), 7.66(1H, br t), 7.67-7.73
 (2H, m), 7.78(1H, d, $J=8.4\text{Hz}$), 7.98(1H, s), 8.58(1H, d, $J=4.9\text{Hz}$).
 IR(KBr) : 1632cm^{-1} .
 mp : 168.5 - 169.5°C .

25

Example 124 (Reference example)

Synthesis of 1-(2,6-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (189)

30 **[0448]** In the same manner as in Example 115, 0.040 g of 1-(2,6-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (189) were formed from 0.600 g of 6-carboxy-1-(2,6-dichlorobenzyl)-2-methylbenzimidazole, 0.472 g of oxalyl chloride, 0.201 g of 2-aminomethylpyridine and 0.188 g of triethylamine.

[0449] Properties of Compound (189):

35 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 2.62(3H, s), 4.76(2H, d, $J=4.7\text{Hz}$), 5.62(2H, s), 7.23(1H, dd, $J=7.1$ and 2.2Hz), 7.28(1H, d,
 $J=7.8\text{Hz}$), 7.32(1H, d, $J=7.9\text{Hz}$), 7.39(2H, d, $J=8.1\text{Hz}$), 7.54(1H, s), 7.66-7.71(3H, m), 7.78(1H, s), 8.60(1H, d,
 $J=4.6\text{Hz}$).
 IR(KBr) : 1635cm^{-1} .
 mp : 225.7 - 226.9°C .

40

Example 125 (Reference example)

Synthesis of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[2-(trifluoromethyl)benzyl]benzimidazole (190)

45 **[0450]** In the same manner as in Example 115, 0.713 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[2-(trifluoromethyl)benzyl]-benzimidazole (190) were formed from 0.970 g of 6-carboxy-2-methyl-1-[2-(trifluoromethyl)benzyl]benzimidazole, 0.736 g of oxalyl chloride, 0.261 g of 2-aminomethylpyridine and 0.726 g of triethylamine.

[0451] Properties of Compound (190):

50 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 2.54(3H, s), 4.76(2H, d, $J=4.8\text{Hz}$), 5.59(2H, s), 6.45(1H, d, $J=7.9\text{Hz}$), 7.22(1H, t, $J=5.8\text{Hz}$),
 7.34(2H, t, $J=8.8\text{Hz}$), 7.40(1H, t, $J=7.5\text{Hz}$), 7.62(1H, br s), 7.68(1H, dt, $J=1.7$ and 7.7Hz), 7.72-7.82(3H, m), 7.87
 (1H, s), 8.56(1H, d, $J=4.9\text{Hz}$).
 IR(KBr) : 1648cm^{-1} .
 mp : 172 - 174°C

55

Example 126 (Reference example)

Synthesis of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(trifluoromethyl)benzyl]benzimidazole (191)

- 5 [0452] In the same manner as in Example 115, 0.194 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(trifluoromethyl)benzyl]benzimidazole (191) were formed from 0.970 g of 6-carboxy-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole, 0.736 g of oxalyl chloride, 0.261 g of 2-aminomethylpyridine and 0.726 g of triethylamine.

[0453] Properties of Compound (191):

- 10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.59(3\text{H}, \text{s}), 4.77(2\text{H}, \text{d}, J=4.7\text{Hz}), 5.45(2\text{H}, \text{s}), 7.15(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.23(1\text{H}, \text{m}), 7.33(1\text{H}, \text{d}, J=7.9\text{Hz}), 7.58(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.63(1\text{H}, \text{br s}), 7.67-7.74(2\text{H}, \text{m}), 7.77(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.93(1\text{H}, \text{s}), 8.57(1\text{H}, \text{d}, J=4.9\text{Hz}).$
 IR(KBr) : 1637 cm⁻¹
 mp : 188.5-190.0°C

Example 127 (Reference example)

Synthesis of 1-(3,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (192)

- 20 [0454] In the same manner as in Example 115, 0.264 g of 1-(3,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (192) were formed from 0.500 g of 6-carboxy-1-(3,4-dichlorobenzyl)-2-methylbenzimidazole, 0.393 g of oxalyl chloride, 0.167 g of 2-aminomethylpyridine and 0.469 g of triethylamine.

[0455] Properties of Compound (192):

- 25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.58(3\text{H}, \text{s}), 4.77(2\text{H}, \text{d}, J=4.8\text{Hz}), 5.33(2\text{H}, \text{s}), 6.85(1\text{H}, \text{dd}, J=8.3 \text{ and } 2.2\text{Hz}), 7.14(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.22(1\text{H}, \text{dd}, J=7.3 \text{ and } 5.6\text{Hz}), 7.33(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.38(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.65-7.77(4\text{H}, \text{m}), 7.92(1\text{H}, \text{d}, J=1.2\text{Hz}), 8.57(1\text{H}, \text{d}, J=4.8\text{Hz}).$
 IR(KBr) : 1638 cm⁻¹.
 mp : 219.0-220.7°C

Example 128 (Reference example)

Synthesis of 2-methyl-1-(2-methylbenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (193)

- 35 [0456] In the same manner as in Example 115, 0.100 g of 2-methyl-1-(2-methylbenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (193) were formed from 0.453 g of 6-carboxy-2-methyl-1-(2-methylbenzyl)benzimidazole, 0.411 g of oxalyl chloride, 0.175 g of 2-aminomethylpyridine and 0.490 g of triethylamine.

[0457] Properties of Compound (193):

- 40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.42(3\text{H}, \text{s}), 2.54(3\text{H}, \text{s}), 4.75(2\text{H}, \text{d}, J=4.9\text{Hz}), 5.32(2\text{H}, \text{s}), 6.33(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.01(1\text{H}, \text{t}, J=7.8\text{Hz}), 7.17-7.24(3\text{H}, \text{m}), 7.33(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.60(1\text{H}, \text{s}), 7.63-7.73(2\text{H}, \text{m}), 7.76(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.84(1\text{H}, \text{d}, J=1.4\text{Hz}), 8.56(1\text{H}, \text{d}, J=4.9\text{Hz}).$
 IR(KBr) : 1635 cm⁻¹.
 mp : 154.0-157.0°C

Example 129 (Reference example)

Synthesis of 1-(2-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (194)

- 50 [0458] In the same manner as in Example 115, 0.918 g of 1-(2-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (194) were formed from 0.997 g of 6-carboxy-1-(2-methoxybenzyl)-2-methylbenzimidazole, 0.858 g of oxalyl chloride, 0.309 g of 2-aminomethylpyridine and 1.02 g of triethylamine.

[0459] Properties of Compound (194):

- 55 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.60(3\text{H}, \text{s}), 3.89(3\text{H}, \text{s}), 4.77(2\text{H}, \text{d}, J=4.8\text{Hz}), 5.36(2\text{H}, \text{s}), 6.60(1\text{H}, \text{d}, J=7.4\text{Hz}), 6.79(1\text{H}, \text{dt}, J=0.8 \text{ and } 7.4\text{Hz}), 6.91(1\text{H}, \text{d}, J=7.4\text{Hz}), 7.20-7.28(2\text{H}, \text{m}), 7.34(1\text{H}, \text{d}, J=7.9\text{Hz}), 7.56(1\text{H}, \text{br t}), 7.66-7.75(3\text{H}, \text{m}), 7.95(1\text{H}, \text{m}), 8.57(1\text{H}, \text{d}, J=4.9\text{Hz}).$
 IR(KBr) : 1652 cm⁻¹.

mp : 136-138.5°C

Example 130 (Reference example)

- 5 Synthesis of 1-(4-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (195)

[0460] In the same manner as in Example 115, 0.697 g of 1-(4-methoxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (195) were formed from 0.985 g of 6-carboxy-1-(4-methoxybenzyl)-2-methylbenzimidazole, 0.858 g of oxalyl chloride, 0.309 g of 2-aminomethylpyridine and 1.02 g of triethylamine.

- 10 [0461] Properties of Compound (195):

¹H-NMR(CDCl₃, δ) : 2.59(3H, s), 3.76(3H, s), 4.78(2H, d, J=4.8Hz), 5.32(2H, s), 6.83(2H, m), 7.00(2H, m), 7.22(1H, dd, J=5.1 and 6.8Hz), 7.34(1H, d, J=7.8Hz), 7.60(1H, br t), 7.67-7.76(3H, m), 7.97(1H, d, J=1.2Hz), 8.57(1H, d, J=4.9Hz).

15 IR(KBr) : 1652cm⁻¹.

mp : 191.5-192.2°C

Example 131 (Reference example)

- 20 Synthesis of 1-[2-(benzenesulfonylmethyl)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (196)

[0462] In the same manner as in Example 115, 0.64 g of 1-[2-(benzenesulfonylmethyl)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (196) were formed from 0.74 g of 1-[2-(benzenesulfonylmethyl)benzyl]-6-carboxy-2-methylbenzimidazole, 0.45 g of oxalyl chloride, 0.19 g of 2-aminomethylpyridine and 0.53 g of triethylamine.

- 25 [0463] Properties of compound (196):

¹H-NMR(CDCl₃, δ) : 2.57(3H, s), 4.50(2H, s), 4.74(2H, d, J=4.9Hz), 5.59(2H, s), 6.63(1H, d, J=7.7Hz), 6.87(1H, d, J=7.4 and 1.5Hz), 7.09-7.19(3H, m), 7.31(1H, d, J=7.8Hz), 7.53-7.61(3H, m), 7.64(1H, dt, J=7.6 and 1.6Hz), 7.68-7.79(5H, m), 7.84(1H, s), 8.52(1H, d, J=4.8Hz).

30 IR(neat) 1646cm⁻¹

liquid.

Example 132 (Reference example)

- 35 Synthesis of 1-(2-cyanobenzyl)-2-methyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (197)

[0464] In the same manner as in Example 115, 1.03 g of 1-(2-cyanobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (197) were formed from 1.14 g of 6-carboxy-1-(2-cyanobenzyl)-2-methylbenzimidazole, 0.998 g of oxalyl chloride, 0.425 g of 2-aminomethylpyridine and 1.19 g of triethylamine.

- 40 [0465] Properties of Compound (197):

¹H-NMR(CDCl₃, δ) : 2.58(3H, s), 4.76(2H, d, J=4.8Hz), 5.59(2H, s), 6.64(1H, d, J=7.4Hz), 7.21(1H, dt, J=5.6 and 1.8Hz), 7.33(1H, d, J=7.9Hz), 7.39-7.47(2H, m), 7.65-7.79(5H, m), 7.89(1H, s), 8.56(1H, dd, J=4.9 and 0.9Hz).

IR(KBr) : 2223, 1642cm⁻¹

45 mp : 150.5-151.4°C

Example 133 (Reference example)

Synthesis of 1-(biphenyl-2-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (198)

- 50 [0466] In the same manner as in Example 115, 0.672 g of 1-(biphenyl-2-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (198) were formed from 1.07 g of 1-(biphenyl-2-ylmethyl)-6-carboxy-2-methylbenzimidazole, 0.796 g of oxalyl chloride, 0.339 g of 2-aminomethylpyridine and 0.950 g of triethylamine.

- 55 [0467] Properties of Compound (198):

¹H-NMR(CDCl₃, δ) : 2.38(3H, s), 4.78(2H, d, J=4.8Hz), 5.27(2H, s), 6.64(1H, d, J=8.0Hz), 7.17-7.24(2H, m), 7.29-7.43(6H, m), 7.48(2H, t, J=5.5Hz), 7.49(1H, s), 7.57-7.73(3H, m), 7.80(1H, d, J=1.0Hz), 8.58(1H, d, J=4.9Hz).

IR(KBr) : 1630, 1619cm⁻¹

mp : 179.8-180.8°C

Example 134 (Reference example)

5 Synthesis of 1-benzyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (199)

[0468] In the same manner as in Example 115, 0.66 g of 1-benzyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (199) were formed from 0.59 g of 1-benzyl-6-carboxy-2-methylbenzimidazole, 0.56 g of oxalyl chloride, 0.24 g of 2-aminomethylpyridine and 0.67 g of triethylamine.

10 [0469] Properties of Compound (199):

¹H-NMR(CDCl₃, δ) : 2.58(3H, s), 4.76(2H, d, J=4.9Hz), 5.36(2H, s), 7.02-7.06(2H, m), 7.21(1H, dd, J=6.9 and 5.0Hz), 7.27-7.35(4H, m), 7.65-7.75(4H, m), 7.96(1H, d, J=0.8Hz), 8.56(1H, d, J=4.8Hz).

IR(KBr) : 1640cm⁻¹.

15 mp : 124.0-124.9°C

Example 135 (Reference example)

Synthesis of 1-(4-tert-butylbenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (200)

20 [0470] In the same manner as in Example 115, 0.477 g of 1-(4-tert-butylbenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (200) were formed from 0.544 g of 1-(4-tert-butylbenzyl)-6-carboxy-2-methylbenzimidazole, 0.428 g of oxalyl chloride, 0.183 g of 2-aminomethylpyridine and 0.511 g of triethylamine.

[0471] Properties of Compound (200):

25 ¹H-NMR(CDCl₃, δ) : 1.27(9H, s), 2.60(3H, s), 4.77(2H, d, J=4.9Hz), 5.34(2H, s), 6.98(2H, d, J=8.3Hz), 7.21(1H, dd, J=7.3 and 5.1Hz), 7.29-7.35(3H, m), 7.62(1H, br s), 7.65-7.75(3H, m), 7.96(1H, d, J=1.1Hz), 8.57(1H, d, J=4.7Hz).

IR(KBr) : 1646cm⁻¹.

30 mp : 140.4-142.8°C

Example 136 (Reference example)

Synthesis of 2-methyl-1-(2-naphthylmethyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (201)

35 [0472] In the same manner as in Example 115, 0.47 g of 2-methyl-1-(2-naphthylmethyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (201) were formed from 0.80 g of 6-carboxy-2-methyl-1-(2-naphthylmethyl)benzimidazole, 0.64 g of oxalyl chloride, 0.27 g of 2-aminomethylpyridine and 0.77 g of triethylamine.

[0473] Properties of Compound (201):

40 ¹H-NMR(CDCl₃, δ) : 2.60(3H, s), 4.75(2H, d, J=4.9Hz), 5.52(2H, s), 7.17-7.23(2H, m), 7.31(1H, d, J=7.8Hz), 7.38 (1H, s), 7.43-7.48(2H, m), 7.60-7.82(7H, m), 8.00(1H, d, J=1.0Hz), 8.53(1H, d, J=4.7Hz).

IR(KBr) : 1640cm⁻¹.

45 mp : 143.0-144.5°C.

Example 137 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (202)

50 [0474] In the same manner as in Example 115, 0.410 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (202) were formed from 0.500 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.356 g of oxalyl chloride, 0.151 g of 2-aminomethylpyridine and 0.424 g of triethylamine.

[0475] Properties of Compound (202):

55 ¹H-NMR(CDCl₃, δ) : 1.45(3H, t, J=7.7Hz), 2.90(2H, q, J=7.4Hz), 4.77(2H, d, J=4.7Hz), 5.43(2H, s), 7.10(2H, d, J=8.2Hz), 7.20(1H, dt, J=4.9 and 7.7Hz), 7.33(2H, t, J=7.4Hz), 7.42(2H, t, J=7.5Hz), 7.49-7.55(4H, m), 7.61(1H, br t), 7.67(1H, dt, J=7.8 and 1.8Hz), 7.72(1H, d, J=8.4Hz), 7.81(1H, d, J=8.4Hz), 7.99(1H, s), 8.56(1H, d, J=4.9Hz). IR(KBr) : 1640cm⁻¹.

mp : 123.0-124.0°C

Example 138 (Reference example)

- 5 Synthesis of 1-(2-chlorobenzyl)-6-[2-(pyridylmethyl)-carbamoyl]benzimidazole (203)

[0476] In the same manner as in Example 115, 0.110 g of 1-(2-chlorobenzyl)-6-[2-(pyridylmethyl)carbamoyl]benzimidazole (203) were formed from 0.461 g of 6-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.728 g of oxalyl chloride, 0.174 g of 2-aminomethylpyridine and 0.486 g of triethylamine.

- 10 [0477] Properties of Compound (203):

¹H-NMR(CDCl₃, δ) : 4.78(2H, d, J=4.8Hz), 5.51(2H, s), 6.92(1H, d, J=6.5Hz), 7.17-7.31(3H, m), 7.34(1H, d, J=7.8Hz), 7.45(1H, dd, J=1.1 and 8.0Hz), 7.69(1H, dt, J=1.8 and 7.7Hz), 7.67-7.73(1H, br s), 7.76(1H, dd, J=1.5 and 8.4Hz), 7.87(1H, d, J=8.4Hz), 8.05(2H, s), 8.57(1H, d, J=4.9Hz).

15 IR(KBr) : 1646cm⁻¹.

mp : 144.0-145.0°C.

Example 139 (Reference example)

- 20 Synthesis of 2-methyl-1-(2-nitrobenzyl)-6-[2-(pyridylmethyl)-carbamoyl]benzimidazole (204)

[0478] In the same manner as in Example 115, 0.241 g of 2-methyl-1-(2-nitrobenzyl)-6-[2-(pyridylmethyl)carbamoyl]benzimidazole (204) were formed from 0.367 g of 6-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 0.299 g of oxalyl chloride, 0.217 g of 2-aminomethylpyridine and 0.360 g of triethylamine.

- 25 [0479] Properties of Compound (204):

¹H-NMR(CDCl₃, δ) : 2.56(3H, s), 4.75(2H, d, J=4.8Hz), 5.83(2H, s), 6.41(1H, d, J=7.8 and 1.2Hz), 7.22(1H, dt, J=5.0 and 1.7Hz), 7.32(1H, d, J=7.9Hz), 7.43-7.52(2H, m), 7.64(1H, s), 7.68(1H, dt, J=7.6 and 1.7Hz), 7.75(1H, dd, J=8.4 and 1.5Hz), 7.80(1H, d, J=8.4Hz), 7.82(1H, d, J=1.3Hz), 8.28(1H, dd, J=8.0 and 1.7Hz), 8.56(1H, d, J=4.9Hz).

IR(KBr) : 1645cm⁻¹.

mp : 194.8-196.7°C

Example 140 (Reference example)

- 35 Synthesis of 2-methyl-1-(2-nitrobenzyl)-5-[2-(pyridylmethyl)-carbamoyl]benzimidazole (205)

[0480] In the same manner as in Example 115, 0.079 g of 2-methyl-1-(2-nitrobenzyl)-5-[2-(pyridylmethyl)carbamoyl]benzimidazole (205) were formed from 0.096 g of 5-carboxy-2-methyl-1-(2-nitrobenzyl)benzimidazole, 0.078 g of oxalyl chloride, 0.048 g of 2-aminomethylpyridine and 0.093 g of triethylamine.

- 40 [0481] Properties of Compound (205):

¹H-NMR(CDCl₃, δ) : 2.57(3H, s), 4.80(2H, d, J=4.7Hz), 5.80(2H, s), 6.43(1H, d, J=7.4 and 0.8Hz), 7.17(1H, d, J=8.4Hz), 7.22(1H, dt, J=5.5 and 1.8Hz), 7.35(1H, d, J=7.8Hz), 7.44-7.52(2H, m), 7.67(1H, s), 7.69(1H, dt, J=7.8 and 1.9Hz), 7.82(1H, dd, J=8.4 and 1.5Hz), 8.27(1H, dd, J=8.0 and 1.6Hz), 8.28(1H, d, J=1.4Hz), 8.56(1H, d, J=4.9Hz).

IR(KBr) : 1645cm⁻¹.

mp : ~96°C(decomp.)

- 50 Example 141

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (206)

[0482] N,N'-carbonyldiimidazole (0.541 g) was added at a time to a solution of 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.689 g of 2-naphthalenesulfonamide and 0.506 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide were added thereto, and the mixture was stirred at 100°C for 48 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue,

and 10% hydrochloric acid was added thereto until the aqueous layer was acidified. The mixture was extracted twice with chloroform. A saturated aqueous solution of sodium hydrogencarbonate was added to the resulting organic layer, and the mixed solution was stirred. The crystals precipitated were separated through filtration, and were dissolved in a small amount of methanol. Further, ethyl acetate was added thereto for crystallization. The crystals were separated through filtration, and were dried to give 0.508 g of 1-(2-chlorobenzyl)-2-methyl-6-(2-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (206).

[0483] Properties of Compound (206):

¹⁰ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.46(3H, s), 5.51(2H, s), 6.38(1H, d, $J=7.9\text{Hz}$), 7.17(1H, t, $J=7.5\text{Hz}$), 7.30(1H, t), 7.45(1H, d, $J=8.5\text{Hz}$), 7.51-7.57(3H, m), 7.77-7.93(5H, m), 7.99(1H, m), 8.35(1H, s).

IR(KBr) : 1594 cm⁻¹.

Mass(FAB) : m/e 512(M+1).

mp : 352.0-354.5°C

Example 142

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)benzimidazole sodium salt (207)

[0484] In the same manner as in Example 141, 0.390 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-naphthalenesulfonylcarbamoyl)-benzimidazole sodium salt (207) were formed from 0.600 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.647 g of N,N'-carbonyldiimidazole, 0.829 g of 1-naphthalenesulfonamide and 0.608 g of diazabicycloundecene.

[0485] Properties of Compound (207):

²⁵ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.46(3H, s), 5.49(2H, s), 6.39(1H, d, $J=7.8\text{Hz}$), 7.16(1H, t, $J=7.5\text{Hz}$), 7.31(1H, t, $J=7.3\text{Hz}$), 7.36(1H, t), 7.40-7.45(2H, m), 7.50(1H, t, $J=7.7\text{Hz}$), 7.54(1H, d, $J=8.0\text{Hz}$), 7.75-7.81(2H, m), 7.87(1H, d, $J=7.9\text{Hz}$), 7.93(1H, d, $J=8.2\text{Hz}$), 8.09(1H, d, $J=7.3\text{Hz}$), 8.86(1H, d, $J=8.5\text{Hz}$).

IR(KBr) : 1633 cm⁻¹.

Mass(FAB) : m/e 512(M+1).

mp : ~265°C(decomp.)

Example 143

Synthesis of 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (208)

[0486] In the same manner as in Example 141, 0.270 g of 6-(4-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (208) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.432 g of N,N'-carbonyldiimidazole, 0.510 g of 4-chlorobenzenesulfonamide and 0.404 g of diazabicycloundecene.

[0487] Properties of Compound (208):

¹⁰ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.46(3H, s), 5.52(2H, s), 6.38(1H, d, $J=7.4\text{Hz}$), 7.19(1H, t, $J=7.6\text{Hz}$), 7.31(1H, t, $J=7.6\text{Hz}$), 7.39(2H, d, $J=8.5\text{Hz}$), 7.45(1H, d, $J=8.9\text{Hz}$), 7.54(1H, d, $J=8.0\text{Hz}$), 7.76-7.82(4H, m).

IR(KBr) : 1592 cm⁻¹.

Mass(FAB) : m/e 496(M+1).

mp : 360-362°C(decomp.)

Example 144

Synthesis of 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (209)

[0488] In the same manner as in Example 141, 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt was obtained from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.573 g of 3-chlorobenzenesulfonamide and 0.456 g of diazabicycloundecene. This salt was dissolved in a mixed solution of methanol and water, and was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.420 g of 6-(3-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (209).

[0489] Properties of Compound (209):

¹H-NMR(DMSO-d₆, δ) : 2.51(3H, s), 5.63(2H, s), 6.48(1H, d, J=7.7Hz), 7.22(1H, t, J=7.6Hz), 7.34(1H, t, J=7.7Hz), 7.56(1H, t, J=8.0Hz), 7.64(1H, t, J=8.0Hz), 7.68(1H, d, J=8.5Hz), 7.78(2H, t, J=8.6Hz), 7.91(1H, d, J=7.6Hz), 7.95(1H, d, J=1.6Hz), 8.10(1H, s).

IR(KBr) : 1687cm⁻¹.

Mass(FAB) : m/e 474(M+1).
mp : 254.5-257.5°C(decomp.)

Example 145

10 Synthesis of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (210)

[0490] In the same manner as in Example 144, 0.447 g of 5-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (210) were formed from 0.466 g of 2-benzyl-5-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.401 g of N,N'-carbonyldiimidazole, 0.389 g of benzenesulfonamide and 0.377 g of diazabicycloundecene.

[0491] Properties of Compound (210):

¹H-NMR(DMSO-d₆, δ) : 4.28(2H, s), 5.57(2H, s), 6.23(1H, d, J=7.6Hz), 7.04(1H, t, J=7.6Hz), 7.10-7.26(6H, m), 7.40(1H, d, J=8.6Hz), 7.46(1H, d, J=8.0Hz), 7.61-7.73(4H, m), 8.00(2H, d, J=7.6Hz), 8.23(1H, s), 12.43(1H, br s).

IR(KBr) : 1685cm⁻¹.

mp : 152.0-155.0°C

Example 146

25 Synthesis of 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (211)

[0492] In the same manner as in Example 144, 0.803 g of 6-benzenesulfonylcarbamoyl-2-benzyl-1-(2-chlorobenzyl)benzimidazole (211) were formed from 0.760 g of 2-benzyl-6-carboxy-1-(2-chlorobenzyl)benzimidazole, 0.654 g of N,N'-carbonyldiimidazole, 0.634 g of benzenesulfonamide and 0.614 g of diazabicycloundecene.

[0493] Properties of Compound (211):

¹H-NMR(DMSO-d₆, δ) : 4.41(2H, s), 5.71(2H, s), 6.32(1H, d, J=7.7Hz), 7.06(1H, t, J=7.7Hz), 7.14-7.30(6H, m), 7.50(1H, d, J=8.0Hz), 7.62(2H, t), 7.70(1H, t), 7.81(1H, d, J=8.6Hz), 7.87(1H, d, J=8.5Hz), 7.97(2H, d, J=8.2Hz), 8.16(1H, s), 12.60(1H, br s).

IR(KBr) : 1704cm⁻¹.

mp : 143.0-144.5°C.

Example 147 (Reference example)

40 Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180)

[0494] Ten milliliters of dichloromethane and 1 drop of N,N-dimethylformamide were added to 0.627 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, and the mixture was cooled with ice. Oxalyl chloride (0.493 g) was added dropwise thereto, and the mixture was stirred for several minutes. Further, the mixture was stirred at room temperature for 1 hour, and was then concentrated under reduced pressure to remove oxalyl chloride. The residue was dissolved in 10 ml of dichloromethane. This solution was added dropwise to a solution of 0.167 g of 2-aminomethylpyridine and 0.469 g of triethylamine in 5 ml of methylene chloride while being cooled with ice. After the mixture was stirred for 1 hour, the reaction solution was washed three times with water and further with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was concentrated under reduced pressure, and was purified through preparative thin-layer silica-gel chromatography (eluent: a mixture of acetone and diethyl ether at a ratio of 1:1). The resulting product was further dissolved in 5 ml of ethyl acetate, and 2 ml of hexane were added thereto for crystallization. The crystals were separated through filtration, and were dried to give 0.359 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (180).

[0495] Properties of Compound (180):

¹H-NMR(CDCl₃, δ) : 2.56(3H, s), 4.76(2H, d, J=4.8Hz), 5.40(2H, s), 6.33(1H, d, J=8.4Hz), 7.07(1H, dd, J=8.4 and 2.0Hz), 7.22(1H, dd, J=7.4 and 4.9Hz), 7.33(1H, d, J=7.9Hz), 7.48(1H, d, J=2.1Hz), 7.62-7.79(4H, m), 7.86(1H, d, J=1.1Hz), 8.57 (1H, d, J=4.9Hz).

IR(KBr) : 1645cm⁻¹.

mp : 204.1-206.3°C

Example 148 (Reference example)

- 5 Synthesis of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (212)

[0496] Oxaly chloride (0.655 g) was added to a solution of 0.886 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methylbenzimidazole and 1 drop of N,N-dimethylformamide in 13 ml of dichloromethane while being cooled with ice, and the mixture was stirred at room temperature for 15 hours. The crystals precipitated were separated through filtration, washed with methylene chloride, and dried under reduced pressure. The crystals were added to a solution of 0.235 g of 2-aminomethylpyridine and 0.653 g of triethylamine in 15 ml of dichloromethane while being cooled, and the mixture was stirred for 1 hour. Water was added to the reaction solution to stop the reaction. The reaction solution was washed twice with water and further with a saturated aqueous solution of sodium hydrogencarbonate. The organic layer was then dried, and the solvent was concentrated under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and ethanol to give 0.774 g of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (212).

[0497] Properties of Compound (212):

20 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.62(3\text{H}, \text{s}), 4.77(2\text{H}, \text{d}, J=4.8\text{Hz}), 5.42(2\text{H}, \text{s}), 7.12(2\text{H}, \text{d}, J=8.5\text{Hz}), 7.21(1\text{H}, \text{m}), 7.34(2\text{H}, \text{m}), 7.42(2\text{H}, \text{m}), 7.51-7.55(4\text{H}, \text{m}), 7.62(1\text{H}, \text{br t}), 7.67(1\text{H}, \text{dt}, J=1.7 \text{ and } 7.7\text{Hz}), 7.71(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.4\text{Hz}), 7.76(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.00(1\text{H}, \text{d}, J=1.2\text{Hz}), 8.56(1\text{H}, \text{d}, J=4.8\text{Hz}).$

IR(KBr) : 1642cm⁻¹.

mp : 205.0-206.5°C

25 Example 149

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

[0498] N,N'-carbonyldiimidazole (0.973 g) was added to a solution of 0.902 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.943 g of benzenesulfonamide and 0.913 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100°C for 70 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The mixed solution was extracted twice with chloroform. The resulting organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was dissolved in a small amount of chloroform, and ethyl acetate was added to the solution for crystallization. The crystals were separated through filtration, and were dried to give 0.667 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

40 Example 150

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole sodium salt (213)

45 [0499] In the same manner as in Example 141, 0.365 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole sodium salt (213) were formed from 0.637 g of 6-carboxy-1-(biphenyl-4-ylmethyl)-2-methylbenzimidazole, 0.533 g of N,N'-carbonyldiimidazole, 0.516 g of benzenesulfonamide and 0.500 g of diazabicycloundecene.

[0500] Properties of Compound (213):

50 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.52(3\text{H}, \text{s}), 5.52(2\text{H}, \text{s}), 7.13(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.31-7.37(4\text{H}, \text{m}), 7.39-7.45(3\text{H}, \text{m}), 7.58-7.63(4\text{H}, \text{m}), 7.78-7.82(3\text{H}, \text{m}), 7.97(1\text{H}, \text{s}).$

IR(Nujol) : 1591cm⁻¹.

mp : 289.0-290.0°C(decomp.)

55

Example 151

Synthesis of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

- 5 [0501] N,N'-carbonyldiimidazole (5.41 g) was added at a time to a solution of 5.02 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 110 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 5.24 g of benzenesulfonamide and 5.08 g of diazabicycloundecene in 20 ml of N,N-dimethylformamide was added thereto, and the mixed solution was stirred at 100°C for 70 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The solution was extracted twice with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and a part of the solvent was distilled off under reduced pressure. The crystals precipitated were separated through filtration, and were dried to give 4.96 g of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163).

15

Example 152

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole hydrochloride (214)

- 20 [0502] N,N'-carbonyldiimidazole (0.647 g) was added at a time to a solution of 0.600 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 20 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.596 g of trifluoromethanesulfonamide and 0.609 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100°C for 72 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, and 10% hydrochloric acid was added thereto while being stirred until the aqueous layer was acidified. The crystals precipitated were washed with a mixed solvent of 25 ml of ethanol and 25 ml of methanol. The crystals were dried to give 0.420 g of 1-(2-chlorobenzyl)-2-methyl-6-trifluoromethanesulfonylcarbamoylbenzimidazole hydrochloride (214).

25

- [0503] Properties of Compound (214):

30

¹H-NMR(DMSO-d6, δ) : 2.84(3H, s), 5.82(2H, s), 7.08(1H, d, J=7.5Hz), 7.30(1H, t), 7.40(1H, t, J=7.7Hz), 7.58(1H, d, J=8.0Hz), 7.79(1H, d, J=8.6Hz), 8.07-8.13(2H, m).

IR(KBr) : 1634cm⁻¹.

Mass(Cl) : m/e 432(M+1-HCl).

35

mp : 332-335°C(decomp.)

Example 153 and 154

- 40 Synthesis of 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole hydrochloride (215) and 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (216)

- 45 [0504] In the same manner as in Example 152, 0.540 g of 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole hydrochloride (215) were formed from 0.460 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.455 g of N,N'-carbonyldiimidazole, 0.431 g of benzenesulfonamide and 0.418 g of diazabicycloundecene.

50

- [0505] Properties of Compound (215):

¹H-NMR(DMSO-d6, δ) : 2.71(3H, s), 5.74(2H, s), 6.83(1H, d, J=8.4Hz), 7.33(1H, dd, J=2.0 and 8.4Hz), 7.63(2H, t), 7.71(1H, t), 7.78(1H, d, J=2.0Hz), 7.86(1H, d, J=8.7Hz), 7.95(1H, dd, J=1.4 and 8.7Hz), 7.99(2H, m), 8.29(1H, s).

IR(KBr) : 1686cm⁻¹.

mp : 236.0-238.0°C

- 55 [0506] This compound was dissolved in a mixed solvent of a potassium hydrogencarbonate and methanol, and the solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, washed with water and with methanol, and dried to give 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (216).

- [0507] Properties of Compound (216):

¹H-NMR(DMSO-d₆, δ) : 2.48(3H, s), 5.58(2H, s), 6.42(1H, d, J=8.4Hz), 7.31(1H, dd, J=2.2 and 8.4Hz), 7.60-7.75(6H, m), 7.99(2H, d, J=7.4Hz), 8.06(1H, s), 12.40(1H, s).
 IR(KBr) : 1540cm⁻¹.
 mp : 238.2.-239.9°C

5

Example 155

Synthesis of 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole (217)

[0508] N,N'-carbodiimidazole (0.431 g) was added at a time to a solution of 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 15 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.498 g of 4-methoxybenzenesulfonamide and 0.405 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixed solution was stirred at 100°C for 67 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being cooled until the aqueous layer was acidified. The resulting mixture was extracted twice with chloroform. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 100:2 to 100:10). The resulting product was concentrated, and was crystallized from a mixed solution of ethyl acetate and diethyl ether. The crystals were separated through filtration, and were dried to give 0.450 g of 1-(2-chlorobenzyl)-6-(4-methoxybenzenesulfonylcarbamoyl)-2-methylbenzimidazole (217).

[0509] Properties of Compound (217):

¹H-NMR(DMSO-d₆, δ) : 2.46(3H, s), 3.83(3H, s), 5.58(2H, s), 7.12(2H, d, J=9.0Hz), 7.21(1H, t, J=7.3Hz), 7.33(1H, t), 7.56(1H, d, J=7.0Hz), 7.63(1H, d, J=8.5Hz), 7.71(1H, dd, J=1.6 and 8.5Hz), 7.91(2H, d, J=9.0Hz), 8.05(1H, d, J=1.3Hz).
 IR(KBr) : 1683cm⁻¹.
 Mass(FAB) : m/e 470(M+1).
 mp : 271.0-274.0°C

30

Example 156

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(α -toluenesulfonylcarbamoyl)benzimidazole (218)

[0510] In the same manner as in Example 155, 0.350 g of 1-(2-chlorobenzyl)-2-methyl-6-(α -toluenesulfonylcarbamoyl)-benzimidazole (218) were formed from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.512 g of α -toluenesulfonamide and 0.456 g of diazabicycloundecene.

[0511] Properties of Compound (218):

¹H-NMR(DMSO-d₆, δ) : 2.48(3H, s), 4.36(2H, s), 5.53(2H, s), 6.40(1H, d, J=6.8Hz), 7.15-7.28(6H, m), 7.32(1H, t), 7.49(1H, d, J=8.3Hz), 7.55(1H, d), 7.83-7.87(2H, m).
 IR(KBr) : 1593cm⁻¹.
 Mass(FAB) : m/e 454(M+1).
 mp : 193-196°C(foamed)

45

Example 157

Synthesis of 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole (219)

[0512] In the same manner as in Example 155, 0.490 g of 1-(2-chlorobenzyl)-6-(2,5-dimethylbenzenesulfonylcarbamoyl)-2-methylbenzimidazole (219) were formed from 0.500 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.539 g of N,N'-carbonyldiimidazole, 0.616 g of 2,5-xylenesulfonamide and 0.506 g of diazabicycloundecene.

[0513] Properties of compound (219):

¹H-NMR(DMSO-d₆, δ) : 2.35(3H, s), 2.48(3H, s), 2.51(3H, s), 5.58(2H, s), 6.45(1H, d, J=7.5Hz), 7.20-7.27(2H, m), 7.31-7.39(2H, m), 7.56(1H, d, J=8.0Hz), 7.64(1H, d, J=8.5Hz), 7.75(1H, d, J=8.5Hz), 7.82(1H, s), 8.06(1H, s), 12.45(1H, br s).
 IR(KBr) : 1690cm⁻¹.

Mass(FAB) : m/e 468(M+1).
mp : 266.5-267.5°C

Example 158

[0514] N,N'-carbodiimidazole (0.432 g) was added at a time to a solution of 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 15 ml of N,N-dimethylformamide, and the solution was stirred at room temperature for 1 hour. Subsequently, a solution of 0.538 g of 4-nitrobenzenesulfonamide and 0.405 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100°C for 84 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Chloroform and hydrochloric acid were added to the residue, and the mixture was stirred to precipitate the crystals. The crystals precipitated were separated through filtration, and were dried to give 0.300 g of 1-(2-chlorobenzyl)-2-methyl-6-(4-nitrobenzenesulfonylcarbamoyl)benzimidazole (220).

[0515] Properties of Compound (220):

¹H-NMR(DMSO-d6, δ) : 2.56(3H, s), 5.65(2H, s), 6.54(1H, d, J=7.6Hz), 7.23(1H, t, J=7.6Hz), 7.34(1H, t, J=7.6Hz), 7.56(1H, t, J=8.0Hz), 7.68(1H, d, J=8.5Hz), 7.83(1H, d, J=8.3Hz), 8.07(1H, s), 8.16(2H, d, J=8.7Hz), 8.37(2H, d, J=8.7Hz).
IR(KBr) : 1621cm⁻¹.
Mass(FAB) : m/e 485(M+1).
mp : 330-332°C

Example 159

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl)-benzenesulfonylcarbamoyl]benzimidazole (221)

[0516] In the same manner as in Example 158, 0.390 g of 1-(2-chlorobenzyl)-2-methyl-6-[4-(trifluoromethyl)benzenesulfonylcarbamoyl]benzimidazole (221) were formed from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.676 g of 4-(trifluoromethyl)-benzenesulfonamide and 0.457 g of diazabicycloundecene.

[0517] Properties of Compound (221):

¹H-NMR(DMSO-d6, δ) : 2.52(3H, s), 5.62(2H, s), 6.47(1H, d, J=7.2Hz), 7.22(1H, t, J=7.5Hz), 7.34(1H, t), 7.56(1H, d, J=8.0Hz), 7.66(1H, d, J=8.5Hz), 7.78(1H, d), 7.97(2H, d, J=8.3Hz), 8.06(1H, s), 8.15(2H, d, J=8.3Hz).
IR(KBr) : 1620cm⁻¹.
Mass(FAB) : m/e 508(M+1).
mp : 288.0-292.0°C

Example 160

Synthesis of 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole ammonium salt (222)

[0518] N,N'-carbonyldiimidazole (0.485 g) was added at a time to a solution of 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole in 15 ml of N,N-dimethylformamide and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.575 g of trifluoromethanesulfonamide and 0.457 g of diazabicycloundecene in 5 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100°C for 72 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue, and 10% hydrochloric acid was added thereto while being mixed until the aqueous layer was acidified. The crystals precipitated were separated through filtration. The crystals were dissolved in ethanol, and the solution was adjusted to a pH of 7 with aqueous ammonia. Further, diisopropylether was added thereto. The crystals precipitated were separated through filtration, and were dried to give 0.360 g of 6-(2-chlorobenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole ammonium salt (222).

[0519] Properties of Compound (222):

¹H-NMR(DMSO-d6, δ) : 2.47(3H, s), 5.51(2H, s), 6.43(1H, d, J=7.5Hz), 7.12(4H, br s), 7.19(1H, t, J=7.6Hz), 7.28-7.38(4H, m), 7.46(1H, d, J=8.3Hz), 7.53(1H, d, J=7.9Hz), 7.78-7.82(2H, m), 7.97(1H, m).

IR(KBr) : 1590cm⁻¹.
 Mass(FAB) : m/e 474(M+1-NH3).
 mp : 264.0-267.0°C

5 Example 161 (Reference example)

Synthesis of 6-carbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (223)

[0520] Oxaly chloride (0.437 g) was added to a solution of 0.490 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 1 drop of N,N-dimethylformamide in 8 ml of methylene chloride while being cooled with ice, and the mixture was stirred at room temperature for 1.5 hours. Four milliliters of 28% aqueous ammonia were added thereto, and the solution was stirred at room temperature for 12 hours. The reaction solution was extracted with the addition of water and methylene chloride. The organic layer was concentrated, and the crystals precipitated were then collected, and were dried to give 0.240 g of 6-carbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (223).

[0521] Properties of Compound (223):

¹H-NMR(DMSO-d6, δ) : 2.48(3H, s), 5.54(2H, s), 6.41(1H, d, J=8.4Hz), 7.21-8.02(3H, m), 7.31(1H, dd, J=2.2 and 8.4Hz), 7.60(1H, d, J=8.4Hz), 7.75(1H, m), 7.93(1H, s).

IR(KBr) : 1666cm⁻¹.

mp : 112.0-114.0°C

Example 162

Synthesis of 6-benzensulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (224)

[0522] N,N'-carbonyldiimidazole (0.248 g) was added at a time to a solution of 0.315 g of 2-benzyl-6-carboxy-1-(2,4-dichlorobenzyl)benzimidazole in 5 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1 hour. Subsequently, a solution of 0.240 g of benzenesulfonamide and 0.233 g of diazabicycloundecene in 4 ml of N,N-dimethylformamide was added thereto, and the mixture was stirred at 100°C for 62 hours. The reaction solution was cooled, and the solvent was distilled off under reduced pressure. Water and chloroform were added to the residue, and 10% hydrochloric acid was added thereto while being mixed until the aqueous layer was acidified. The solution was extracted twice with chloroform. The resulting organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, and a part of the solvent was distilled off under reduced pressure. To the residue were added 4 ml of methanol and 4 ml of a 20% potassium hydrogen carbonate aqueous solution to form a uniform solution. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.310 g of 6-benzensulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (224).

[0523] Properties of Compound (224):

¹H-NMR(DMSO-d6, δ) : 4.32(1H, s), 5.61(2H, s), 6.16(1H, d, J=8.4Hz), 7.09(1H, dd, J=8.4 and 1.9Hz), 7.18-7.10(5H, m), 7.82-7.58(6H, m), 7.97(2H, d, J=7.6Hz), 8.10(1H, s), 12.43(1H, br s).

IR(KBr) : 1703cm⁻¹.

mp : 236.0-238.0°C

Example 163

Synthesis of 5-benzensulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (225)

[0524] In the same manner as in Example 152, 0.270 g of 5-benzensulfonylcarbamoyl-2-benzyl-1-(2,4-dichlorobenzyl)benzimidazole (225) were formed from 0.385 g of 2-benzyl-5-carboxy-1-(2,4-dichlorobenzyl)benzimidazole, 0.304 g of N,N'-carbonyldiimidazole, 0.294 g of benzenesulfonamide and 0.285 g of diazabicycloundecene.

[0525] Properties of Compound (225):

¹H-NMR(DMSO-d6, δ) : 4.28(2H, s), 5.52(2H, s), 6.14(1H, d, J=8.4Hz), 7.21-7.06(6H, m), 7.42(1H, d, J=8.6Hz), 7.76-7.57(5H, m), 8.05-7.95(2H, m), 8.24(1H, s), 12.43(1H, br s).

IR(KBr) : 1691cm⁻¹.

mp : 107.0-110.0°C.

Example 164

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-hydroxybenzimidazole (226)

- 5 [0526] Tetramethoxymethane (0.220 g) was added to a solution of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 5 ml of acetic acid, and the mixture was stirred at 80 °C for 2 hours. The reaction solution was concentrated, and a 20% potassium hydrogencarbonate aqueous solution was added to this reaction solution to render it basic. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, and 10 ml of methanol, 0.50 g of 10% hydrochloric acid and 0.35% hydrochloric acid were added thereto. The mixture was stirred at 60°C for 15 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the solution to render it alkaline. This solution was then adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.219 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-hydroxybenzimidazole (226).
- 10 [0527] Properties of Compound (226):

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 5.07(2\text{H}, \text{s}), 7.08(1\text{H}, \text{d}, J=8.2\text{Hz}), 7.33-7.39(3\text{H}, \text{m}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.60-7.65(7\text{H}, \text{m}), 7.66-7.72(2\text{H}, \text{m}), 7.96-7.80(2\text{H}, \text{m}), 11.46(1\text{H}, \text{s}), 12.34(1\text{H}, \text{s}).$
 IR(KBr) : 1704, 1686 cm⁻¹.
 Mass(FD) : m/e 483(M).
 mp : 268.7-273.9°C

Example 165

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole (227)

- 25 [0528] Two milliliters of carbon disulfide were added to a solution of 0.800 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, and the mixture was stirred at 50°C for 70 hours. Chloroform and water were added thereto. The crystals precipitated were separated through filtration, and were dried to give 0.719 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptobenzimidazole (227).
- 30 [0529] Properties of Compound (227):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 5.55(2\text{H}, \text{s}), 7.28(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.35(1\text{H}, \text{t}, J=6.3\text{Hz}), 7.39-7.47(4\text{H}, \text{m}), 7.61-7.65(6\text{H}, \text{m}), 7.69(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.78(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.4\text{Hz}), 7.87(1\text{H}, \text{s}), 7.81-7.98(2\text{H}, \text{m}), 12.51(1\text{H}, \text{s}), 13.29(1\text{H}, \text{s}).$
 IR(KBr) : 1701 cm⁻¹.
 mp : 320.0-321.0°C

Example 166

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole (228)

- 40 [0530] Tetramethoxymethane (0.250 g) was added to a solution of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 3 ml of acetic acid, and the mixture was stirred at 80°C for 2 hours. Methanol was added to the reaction solution, and the crystals precipitated were collected. The crystals were washed with a mixed solvent of 1 ml of acetone and 8 ml of methanol, separated through filtration, and dried to give 0.280 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxybenzimidazole (228).
- 45 [0531] Properties of Compound (228):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 4.17(3\text{H}, \text{s}), 5.33(2\text{H}, \text{s}), 7.30(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.50(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.60-7.65(6\text{H}, \text{m}), 7.68-7.72(2\text{H}, \text{m}), 7.98-8.01(2\text{H}, \text{m}), 8.05(1\text{H}, \text{d}, J=1.5\text{Hz}), 8.18(1\text{H}, \text{s}), 12.50(1\text{H}, \text{s}).$
 IR(KBr) : 1690 cm⁻¹.
 mp : 136.0-138.5°C

Example 167

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole (229)

- 55 [0532] Triethylamine (0.080 g) and 0.148 g of methyloxalyl chloride were added to a solution of 0.400 g of N-ben-

nesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 3 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain crude 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole. This compound was dissolved in 1 ml of acetic acid and 5 ml of methanol, and the mixture was stirred at 60°C for 15 hours. The reaction solution was neutralized with a potassium hydroxide aqueous solution. The crystals precipitated were separated through filtration, and were dried to give 0.245 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-carboxybenzimidazole (229).

[0533] Properties of Compound (229):

¹⁰ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 5.44(2H, s), 7.23(1H, d, $J=8.4\text{Hz}$), 7.36(1H, t, $J=7.6\text{Hz}$), 7.41(2H, d, $J=8.1\text{Hz}$), 7.45(2H, t, $J=7.5\text{Hz}$), 7.58(2H, t, $J=7.8\text{Hz}$), 7.60-7.71(7H, m), 7.94(2H, d, $J=8.3\text{Hz}$), 12.38(1H, s), 12.52(1H, s).
 IR(KBr) : 1670cm⁻¹.
 mp : 247.5-250.0°C

¹⁵ Example 168

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole (230)

[0534] A mixture containing 0.300 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.200 g of methyl isothiocyanate, 5 ml of methanol and 5 ml of acetone was stirred at room temperature for 12 hours. Further, 1 ml of 97% sulfuric acid was added thereto, and the mixture was stirred at room temperature for 43 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the reaction solution to render it basic. This reaction solution was then concentrated, and the residue was extracted with ethyl acetate and with water. The organic layer was concentrated, dissolved in chloroform, and precipitated with hexane. The crystals precipitated were separated through filtration, and were dried to give 0.140 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylaminobenzimidazole (230).

[0535] Properties of Compound (230):

³⁰ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.98(3H, d, $J=4.4\text{Hz}$), 5.34(2H, s), 7.22(2H, d, $J=8.2\text{Hz}$), 7.26(1H, d, $J=8.4\text{Hz}$), 7.34(1H, t, $J=7.3\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.57(2H, t, $J=7.6\text{Hz}$), 7.59-7.68(6H, m), 7.76(1H, s), 7.95(2H, d, $J=7.4\text{Hz}$), 12.28(1H, s).
 IR(KBr) : 1672cm⁻¹.
 Mass(FAB) : m/e 497(M+1).
 mp : 225.0-228.0°C

³⁵ Example 169

Synthesis of 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (231)

[0536] Ten milliliters of methanol, 10 ml of acetone and 0.395 g of cyanogen bromide were added to 1.500 g of N-benzenesulfonylcarbamoyl-4-amino-3-(biphenyl-4-ylmethylamino)-benzamide, and the mixture was stirred at room temperature for 100 hours and then at 50°C for 30 hours. The reaction solution was extracted with chloroform and with water. The organic layer was washed six times with water, and was concentrated. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to give 0.135 g of 2-amino-6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (231).

[0537] Properties of Compound (231):

⁵⁰ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 5.32(2H, s), 6.77(2H, s), 7.05(1H, d, $J=8.8\text{Hz}$), 7.21(2H, d, $J=8.3\text{Hz}$), 7.31-7.38(4H, m), 7.43(2H, t, $J=7.5\text{Hz}$), 7.58-7.65(6H, m), 7.79-7.82(2H, m).
 IR(KBr) : 1684cm⁻¹.
 Mass(FAB) : m/e 483(M+1).
 mp : 352.5-355.0°C

⁵⁵ Example 170

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole potassium salt (232)

[0538] Triethylamine (0.060 g) and 0.084 g of butyryl chloride were added to a solution of 0.300 g of N-benzenesul-

fonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 2 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 1.5 hours. The reaction solution was directly purified through silica-gel column chromatography to obtain 0.250 g of N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-butyrylaminobenzamide. To this compound were added 5 ml of methanol and 0.50 g of 35% hydrochloric acid, and the mixture was stirred at 60°C for 3 hours.

5 Then, 20% potassium hydrogencarbonate was added thereto to stop the reaction, and the reaction solution was extracted with ethyl acetate and with water. The organic layer was concentrated, and the product was dissolved in a small amount of chloroform. Ether was added thereto for crystallization. The crystals precipitated were separated through filtration, and were dried to give 0.157 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylbenzimidazole potassium salt (232).

10 [0539] Properties of Compound (232):

¹H-NMR(DMSO-d₆, δ) : 0.95(3H, t, J=7.4Hz), 1.77(2H, q, J=7.5Hz), 2.82(2H, t, J=7.5Hz), 5.55(2H, s), 7.11(2H, d, J=8.2Hz), 7.32-7.38(4H, m), 7.43(2H, t, J=7.5Hz), 7.47(1H, d, J=8.4Hz), 7.58-7.64(4H, m), 7.79-7.83(3H, m), 7.96 (1H, s).

15 IR(Nujol) : 1592cm⁻¹.

Mass(FAB) : m/e 548(M+1).

mp : 279.0-282.0°C

Example 171

20 Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole (233)

[0540] In the same manner as in Example 170, 0.232 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-heptylbenzimidazole (233) were formed from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.080 g of triethylamine and 0.170 g of octanoyl chloride.

25 [0541] Properties of Compound (233):

¹H-NMR(DMSO-d₆, δ) : 0.79(3H, t, J=7.3Hz), 1.12-1.24(6H, m), 1.24-1.31(2H, m), 1.66-1.73(2H, m), 2.84(2H, t, J=7.6Hz), 5.58(2H, s), 7.14(2H, d, J=8.1Hz), 7.34(2H, t, J=7.6Hz), 7.43(2H, t, J=7.4Hz), 7.52-7.66(7H, m), 7.75 (1H, d, J=8.8Hz), 7.95(2H, d, J=7.6Hz), 8.15(1H, s), 12.45(1H, s).IR(KBr) : 1688cm⁻¹.

mp : 112.0-117.5°C

Example 172

35 Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole (234)

[0542] In the same manner as in Example 170, 0.913 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-chloromethylbenzimidazole (234) were formed from 0.300 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.060 g of triethylamine and 0.102 of chloroacetyl chloride.

40 [0543] Properties of Compound (234):

¹H-NMR(DMSO-d₆, δ) : 5.10(2H, s), 5.71(2H, s), 7.23(2H, d, J=8.3Hz), 7.35(1H, t, J=7.3Hz), 7.44(2H, t, J=7.5Hz), 7.60-7.66(6H, m), 7.69(1H, t, J=7.5Hz), 7.75-7.81(2H, m), 7.98-8.01(2H, m), 8.16(1H, s), 12.52(1H, s).

45 IR(KBr) : 1700cm⁻¹.

mp : 220.5-223.5°C.

Example 173

50 Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole (235)

[0544] In the same manner as in Example 170, 0.183 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methoxymethylbenzimidazole (235) were formed from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide, 0.115 g of triethylamine and 0.131 g of methoxyacetyl chloride.

55 [0545] Properties of Compound (235):

¹H-NMR(DMSO-d₆, δ) : 3.31(3H, s), 4.72(2H, s), 5.63(2H, s), 7.23(2H, d, J=8.3Hz), 7.35(1H, t, J=7.4Hz), 7.44(2H, t, J=7.5Hz), 7.60-7.65(6H, m), 7.70(1H, t, J=7.5Hz), 7.72-7.79(2H, m), 7.98-8.01(2H, m), 8.18(1H, s), 12.50(1H, s).IR(KBr) : 1690cm⁻¹.

mp : 195.0-198.0°C.

Example 174

5 Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole potassium salt (236)

[0546] In the same manner as in Example 170, 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino) benzamide, 0.080 g of triethylamine and 0.112 g of isobutyryl chloride were reacted as starting materials. The crude product was dissolved in a mixed solvent of methanol and a 20 % potassium hydrogencarbonate aqueous solution, and the pH was adjusted to 7 with 10% hydrochloric acid. The crystals precipitated were crystals of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-i-propylbenzimidazole potassium salt [(236), 0.167 g].

10 [0547] Properties of Compound (236):

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 1.26(6H, d, $J=6.8\text{Hz}$), 3.25-3.40(1H, m), 5.58(2H, s), 7.09(2H, d, $J=8.3\text{Hz}$), 7.32-7.37(4H, m), 7.43(2H, t, $J=7.5\text{Hz}$), 7.48(1H, d, $J=8.4\text{Hz}$), 7.58-7.64(4H, m), 7.79-7.83(3H, m), 7.95(1H, s).

IR(Nujol) : 1592cm⁻¹.

Mass(FAB) : m/e 548(M+1).

mp : 310.1-312.7°C.

Example 175

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylthiobenzimidazole (237)

[0548] A 20% potassium hydroxide aqueous solution (0.323 g), 2 ml of water and 0.123 g of methyl iodide were added to a solution of 0.310 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptopbenzimidazole in 5 ml of methanol in this order, and the mixture was stirred at room temperature for 2 hours. The reaction solution was adjusted to a pH of from 5 to 6 with 10 % hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.281 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-methylthiobenzimidazole (237).

30 [0549] Properties of Compound (237):

1H-NMR(DMSO-d₆, δ) : 2.75(3H, s), 5.48(2H, s), 7.25(2H, d, $J=8.3\text{Hz}$), 7.35(1H, t, $J=7.4\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.60-7.66(7H, m), 7.68-7.75(2H, m), 7.82-7.99(2H, m), 8.19(1H, d, $J=1.6\text{Hz}$), 12.43(1H, s).

IR(KBr) : 1685cm⁻¹.

mp : 218.8-220.4°C.

Example 176

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole (238)

[0550] In the same manner as in Example 175, 0.225 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-ethylthiobenzimidazole (238) were formed from 0.240 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptopbenzimidazole and 0.117 g of ethyl iodide.

[0551] Properties of Compound (238):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 1.39(3H, t, $J=7.3\text{Hz}$), 3.37(2H, q, $J=7.3\text{Hz}$), 5.47(2H, s), 7.24(2H, d, $J=8.1\text{Hz}$), 7.35(1H, t, $J=7.1\text{Hz}$), 7.44(2H, t, $J=7.6\text{Hz}$), 7.57-7.68(8H, m), 7.75(1H, d, $J=8.4\text{Hz}$), 7.98(2H, d, $J=7.5\text{Hz}$), 8.15(1H, s), 12.43(1H, s).

IR(KBr) : 1686cm⁻¹.

50 mp : 125.5-129.5°C.

Example 177

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole (239)

55 [0552] In the same manner as in Example 175, 0.156 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-propylthiobenzimidazole (239) were formed from 0.220 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptopbenzimidazole and 0.117 g of n-propyl iodide.

[0553] Properties of Compound (239):

⁵ ¹H-NMR(DMSO-d₆, δ) : 0.97(3H, t, J=7.4Hz), 1.76(2H, q, J=7.2Hz), 3.29-3.36(2H, m), 5.48(2H, s), 7.24(2H, d, J=8.3Hz), 7.35(1H, t, J=7.3Hz), 7.44(2H, t, J=7.4Hz), 7.58-7.71(8H, m), 7.74(1H, dd, J=8.5 and 1.7Hz), 7.99(2H, d, J=7.7Hz), 8.17(1H, s), 12.43(1H, s).
IR(KBr) : 1690cm⁻¹.
mp : 106.0-111.5°C.

Example 178

¹⁰ Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole (240)

[0554] In the same manner as in Example 175, 0.212 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-n-hexylthiobenzimidazole (240) were formed from 0.250 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-mercaptopbenzimidazole and 0.166 g of n-hexyl iodide.

[0555] Properties of Compound (240):

¹⁵ ¹H-NMR(DHSO-d₆, δ) : 0.82(3H, t, J=7.9Hz), 1.19-1.33(4H, m), 1.33-1.44(2H, m), 1.68-1.75(2H, m), 3.30-3.43(2H, m), 5.48(2H, s), 7.23(2H, d, J=8.2Hz), 7.35(1H, t, J=7.1Hz), 7.44(2H, t, J=7.6Hz), 7.60-7.75(9H, m), 8.00(2H, d, J=7.7Hz), 8.19(1H, s), 12.44(1H, s).
IR(KBr) : 1688cm⁻¹.
mp : 139.5-141.0°C(decomp.)

Example 179

²⁵ Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-benzimidazole (241)

[0556] A mixture of 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide and 2 ml of formic acid was stirred at 90°C for 3 hours. The reaction solution was concentrated, and was precipitated with methanol. The crystals precipitated were separated through filtration, and were dried to give 0.243 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)benzimidazole (241).

[0557] Properties of Compound (241):

³⁰ ¹H-NMR(DMSO-d₆, δ) : 5.60(2H, s), 7.35(1H, t, J=7.2Hz), 7.39(2H, d, J=8.2Hz), 7.44(2H, t, J=7.6Hz), 7.61-7.77(9H, m), 8.00(2H, d, J=7.7Hz), 8.26(1H, s), 8.66(1H, s), 12.5(1H, s).
IR(KBr) : 1683cm⁻¹.
mp : 141.5-143.6°C.

Example 180 (Reference example)

⁴⁰ Synthesis of 1-(4-benzyloxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (242)

[0558] Four milliliters of acetic acid and 8 ml of ethanol were added to 0.434 g of N-(2-pyridylmethyl)-4-acetylaminio-3-(4-benzyloxybenzylamino)benzamide, and the mixture was stirred at 90°C for 7 hours. The reaction solution was concentrated under reduced pressure. Ethyl acetate and ether were added to the residue for crystallization. The crystals were separated through filtration, and were dried to give 0.375 g of 1-(4-benzyloxybenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (242).

[0559] Properties of Compound (242):

⁵⁰ ¹H-NMR(CDCl₃, δ) : 2.59(3H, s), 4.78(2H, d, J=4.8Hz), 5.01(2H, s), 5.31(2H, s), 6.89(2H, d, J=8.7Hz), 6.99(2H, d, J=8.6Hz), 7.21(1H, dd, J=5.1 and 7.4Hz), 7.29-7.42(6H, m), 7.62(1H, br t), 7.65-7.75(3H, m), 7.98(1H, s), 8.57(1H, d, J=4.1Hz).
IR(KBr) : 1640cm⁻¹.
mp : 169.0-170.0°C.

Example 181 (Reference example)

Synthesis of 2-methyl-1-(3,4-methylenedioxybenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (243)

- 5 [0560] Two milliliters of acetic acid and 5 ml of methanol were added to 0.490 g of N-(2-pyridylmethyl)-4-acetylamino-3-(3,4-methylenedioxybenzylamino)benzamide, and the mixture was stirred at 70°C for 8 hours. The reaction solution was concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1), and was then crystallized from ethyl acetate. The crystals were separated through filtration, and were dried to give 0.270 g of 2-methyl-1-(3,4-methylenedioxybenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (243).
- 10 [0561] Properties of Compound (243):

¹H-NMR(CDCl₃, δ) : 2.59(3H, s), 4.78(2H, d, J=4.8Hz), 5.28(2H, s), 5.93(2H, s), 6.51(1H, d, J=1.6Hz), 6.55(1H, dd, J=1.4 and 7.9Hz), 6.72(2H, d, J=8.0Hz), 7.22(1H, dd, J=6.7 and 5.0Hz), 7.34(1H, d, J=7.7Hz), 7.62(1H, br t), 7.67-7.75(3H, m), 7.96(1H, d, J=1.1Hz), 8.58(1H, d, J=4.9Hz).
 IR(KBr) : 1637cm⁻¹.
 mp : 190.5-192.0°C.

Example 182 (Reference example)

Synthesis of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (244)

- 20 [0562] In the same manner as in Example 180, 0.33 g of 2-methyl-6-[(2-pyridylmethyl)carbamoyl]-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (244) were formed from 0.50 g of N-(2-pyridylmethyl)-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl)benzylamino]benzamide.
- 25 [0563] Properties of Compound (244):

¹H-NMR(CDCl₃, δ) : 2.58(3H, s), 4.58(2H, d, J=5.9Hz), 5.62(2H, s), 7.24(1H, dd, J=7.3 and 5.0Hz), 7.28-7.33(3H, m), 7.64(1H, d, J=8.4Hz), 7.73(1H, dt, J=7.7 and 1.6Hz), 7.81(1H, dd, J=8.4 and 1.3Hz), 8.10(1H, d, J=8.2Hz), 8.13(1H, s), 8.49(1H, d, J=4.2Hz), 9.04(1H, t, J=5.9Hz), 9.58(1H, s).
 IR(KBr) : 1642cm⁻¹.
 mp : 216.0-217.0°C.

Example 183

Synthesis of 6-benzenesulfonylcaramoyl-1-(2,4-difluorobenzyl)-2-methylbenzimidazole (245)

- 35 [0564] N-benzenesulfonyl-4-acetylamino-3-(2,4-difluorobenzylamino)benzamide (0.370 g) was dissolved in a mixed solvent of 3.3 g of 10% hydrochloric acid, 6 ml of methanol and 4 ml of water, and 0.5 g of 35% hydrochloric acid were further added thereto. The mixture was stirred at 60°C for 3 hours. A 20% potassium hydrogencarbonate aqueous solution was added to the reaction solution to render it basic. Then, this solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and were dried to give 0.182 g of 6-benzenesulfonylcaramoyl-1-(2,4-difluorobenzyl)-2-methylbenzimidazole (245).
- 40 [0565] Properties of Compound (245):

¹H-NMR(DMSO-d6, δ) : 2.53(3H, s), 5.56(2H, s), 6.95-7.01(1H, m), 7.04(1H, dt, J=8.7 and 1.4Hz), 7.32(1H, dt, J=10.7 and 2.1Hz), 7.59-7.66(3H, m), 7.68-7.74(2H, m), 8.00(2H, d, J=8.1Hz), 8.13(1H, s), 12.43(1H, s).IR(KBr) : 1686cm⁻¹.
 mp : 234.5-235.5°C(decomp.)

Example 184

Synthesis of 6-benzenesulfonylcaramoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole (246)

- 50 [0566] Triethylamine (0.115g) and 0.200 g of benzoyl chloride were added to a solution of 0.500 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide in 5 ml of N,N-dimethylformamide. The mixture was stirred at room temperature for 15 hours. A potassium hydrogencarbonate aqueous solution was added thereto to stop the reaction. The solvent was distilled off under reduced pressure. The residue was dissolved in a mixture of water and

methanol, and the solution was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were collected, and were dried to obtain 0.393 g of crude N-benzenesulfonyl-4-benzoylamino-3-(biphenyl-4-ylmethylamino)benzamide. This crude product was converted to 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-phenylbenzimidazole [(246), 0.270 g] in the same manner as in Example 183.

5 [0567] Properties of Compound (246):

¹H-NMR(DMSO-d₆, δ) : 5.70(2H, s), 7.07(2H, d, J=8.2Hz), 7.32-7.37(1H, m), 7.43(2H, t, J=5.7Hz), 7.53-7.58(2H, m), 7.58-7.65(7H, m), 7.68-7.72(1H, m), 7.77(2H, dd, J=7.5 and 1.5Hz), 7.81-7.83(2H, m), 7.98-8.02(2H, m), 8.22(1H, s), 12.47(1H, s).
IR(KBr) : 1690cm⁻¹.
mp : 138.5-139.5°C.

Example 185

15 Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (247)

[0568] In the same manner as in Example 183, 0.237 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-(2-nitrobenzyl)benzimidazole (247) were formed from 0.79 g of N-benzenesulfonyl-4-acetylamino-3-(2-nitrobenzylamino)benzamide.

[0569] Properties of Compound (247):

¹H-NMR(DMSO-d₆, δ) : 2.48(3H, s), 5.01(2H, s), 5.93(2H, s), 6.28-6.30(1H, m), 7.55-7.62(4H, m), 7.64-7.74(3H, m), 7.97(2H, d, J=8.0Hz), 8.10(1H, s), 8.22-8.28(1H, m), 12.39(1H, s).
IR(KBr) : 1686cm⁻¹.
mp : 269.5-272.5°C (decomp.)

Example 186

Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-benzylbenzimidazole (248)

30 [0570] In the same manner as in Example 183, 0.222 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-benzylbenzimidazole (248) were formed from 0.38 g of N-benzenesulfonyl-4-acetylamino-3-benzylaminobenzamide.

[0571] Properties of Compound (248):

¹H-NMR(DMSO-d₆, δ) : 2.54(3H, s), 5.55(2H, s), 7.12(2H, d, J=7.9Hz), 7.28(1H, t, J=7.3Hz), 7.34(2H, t, J=7.0Hz), 7.61-7.66(3H, m), 7.69-7.76(2H, m), 8.00(2H, d, J=7.9Hz), 8.18(1H, s), 12.43(1H, s).
IR(KBr) : 1695cm⁻¹.
mp : 260.0-262.0°C(decomp.)

Examples 187 and 188

40 Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole (249) and 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole potassium salt (250)

[0572] In the same manner as in Example 183, 0.255 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole (249) were formed as a crystal from 0.505 g of N-benzenesulfonyl-4-acetylamino-3-(4-nitrobenzylamino)benzamide. Further, the filtrate was concentrated to form 0.136 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-(4-nitrobenzyl)benzimidazole potassium salt (250) as a crystal.

[0573] Properties of Compound (249):

¹H-NMR(DMSO-d₆, δ) : 2.50(3H, s), 5.70(2H, s), 7.30(2H, d, J=8.7Hz), 7.52(2H, t, J=7.6Hz), 7.57(2H, d, J=8.3Hz), 7.76(1H, dd, J=8.4 and 1.4Hz), 7.92(2H, d, J=7.3Hz), 8.05(1H, s), 8.20(2H, d, J=8.7Hz), 12.43(1H, s).
IR(KBr) : 1686cm⁻¹.
mp : 164.5-167.0°C.

55 [0574] Properties of Compound (250):

¹H-NMR(DMSO-d₆, δ) : 2.51(3H, s), 5.68(2H, s), 7.28(2H, d, J =8.5Hz), 7.32-7.41(3H, m), 7.46(1H, d, J=8.4Hz), 7.78-7.86(3H, m), 7.91(1H, s), 8.20(2H, d, J=8.5Hz).

IR(KBr) : 1594cm⁻¹.
mp : 326.0-328.0°C(decomp.)

Example 189

5 **[0575]** A mixture containing 0.500 g of N-benzenesulfonyl-3-amino-4-acetylaminobenzamide potassium salt, 0.470 g of 4-benzyloxybenzyl bromide, 0.925 g of a 20 % potassium hydrogencarbonate aqueous solution and 3 ml of N,N-dimethylformamide was stirred at 90°C for 1 hour. The reaction solution was concentrated, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain crude N-benzenesulfonyl-4-acetylaminoo-3-(4-benzyloxybenzylamino)benzamide. This crude product was cyclized in the same manner as in Example 183 to give 0.160 g of 6-benzenesulfonylcarbamoyl-1-(4-benzyloxybenzyl)-2-methylbenzimidazole (251).

10 **[0576]** Properties of Compound (251):

15 ¹H-NMR(DMSO-d6, δ) : 2.54(3H, s), 5.05(2H, s), 5.44(2H, s), 7.09(2H, d, J=8.7Hz), 7.32(2H, d, J=7.0Hz), 7.29-7.44(5H, m), 7.58-7.67(3H, m), 7.68-7.75(2H, m), 7.79-8.02(2H, m), 8.18(1H, s), 12.46(1H, s).
IR(KBr) : 1685cm⁻¹.
20 mp : 111.0-114.0°C.

Example 190 (Reference example)

25 Synthesis of 2-methyl-5-[(2-pyridylmethyl)carbamoyl]-benzimidazole (252)

30 **[0577]** Five-percent palladium on carbon (0.10 g) was added to a mixture of 1.00 g of crude N-(2-pyridylmethyl)-4-acetylamino-3-nitrobenzamide, 8 ml of acetic acid and 12 ml of ethanol, and the solution was stirred in a hydrogen atmosphere at 80°C for 7 hours. The solid material was separated through filtration, and the filtrate was concentrated. Ethyl acetate was added to the residue for crystallization. The crystals were separated through filtration, and were dried to give 0.57 g of 2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (252).

35 **[0578]** Properties of Compound (252):

40 ¹H-NMR(CDCl₃, δ) : 2.52(3H, s), 4.59(2H, d, J=5.9Hz), 7.26(1H, dd, J=7.1 and 5.1Hz), 7.33(1H, d, J=7.8Hz), 7.50(1H, d, J=8.4Hz), 7.72-7.78(2H, m), 8.08(1H, s), 8.51(1H, d, J=4.8Hz), 9.04(1H, t, J=5.8Hz), 12.44(1H, s).
IR(KBr) : 1641cm⁻¹.
45 mp : 212.0-215.0°C.

Examples 191 and 192 (Reference examples)

50 **40** Synthesis of 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (253) and 1-benzenesulfonyl-2-methyl-5-[2-pyridylmethyl)carbamoyl]benzimidazole (254)

55 **[0579]** Ten milliliters of dichloromethane and 0.760 g of triethylamine were added to 1.00 g of 1-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole, and 0.994 g of benzenesulfonyl chloride were added dropwise thereto. The mixture was stirred for 3 hours, and the reaction solution was washed three times with water and then with a sodium hydrogencarbonate aqueous solution. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 9:1) to obtain 1.380 g of a mixture of 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl) carbamoyl]benzimidazole and 1-benzenesulfonyl-2-methyl-5-[2-pyridylmethyl)carbamoyl]benzimidazole. This mixture was further purified through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 100:3) to give 0.550 g of oily 1-benzenesulfonyl-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (253) and 0.540 g of oily 1-benzenesulfonyl-2-methyl-5-[2-pyridylmethyl)carbamoyl]benzimidazole (254). These oily products were dissolved in 1.5 ml of methylene chloride, and were crystallized from diethyl ether.

55 **[0580]** Properties of Compound (253):

60 ¹H-NMR(CDCl₃, δ) : 2.84(3H, s), 4.81(2H, d, J=4.8Hz), 7.24(1H, dd, J=5.1 and 7.3Hz), 7.37(1H, d, J=7.7Hz), 7.53(2H, dd, J=7.9 and 7.5Hz), 7.63-7.74(2H, m), 7.85(1H, dd, J=8.4 and 1.2Hz), 7.97(2H, dd, J=9.6 and 1.1Hz), 8.58-8.61(2H, m).

IR(KBr) : 1636cm⁻¹.
mp : 163.4-164.3°C.

[0581] Properties of Compound (254):

⁵ ¹H-NMR(CDCl₃, δ): 2.83(3H, s), 4.78(2H, d, J=4.7Hz), 7.23(1H, dd, J=4.9 and 8.6Hz), 7.34(1H, d, J=7.9Hz), 7.53(2H, dd, J=7.5 and 8.4Hz), 7.64-7.75(3H, m), 7.91-7.96(3H, m), 8.10(1H, d, J=9.1Hz), 8.14(1H, d, J=1.3Hz), 8.56(1H, dd, J=4.9 and 1.0Hz).

IR(KBr) : 1657cm⁻¹.
¹⁰ mp : 88.3-91.3°C.

Examples 193 and 194 (Reference examples)

Synthesis of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (255) and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (256)

[0582] Ten milliliters of N,N-dimethylformamide, 3.24 g of 4-nitrobenzyl bromide and 2.52 g of sodium hydrogencarbonate were added to 3.56 g of 2-methyl-5-[2-pyridylmethyl)-carbamoyl]benzimidazole, and the mixture was heated at 80°C for 2 hours. The reaction solution was separated with the addition of chloroform and water. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 4:1) to obtain a mixture of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole. This mixture was further separated into position isomers through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 85:15). Each of the position isomers was recrystallized from a mixed solvent of chloroform and diethyl ether to give 1.37 g of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (255) and 1.19 g of 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (256).

[0583] Properties of Compound (255):

³⁰ ¹H-NMR(CDCl₃, δ) : 2.59(3H, s), 4.77(2H, d, J=4.8Hz), 5.48(2H, s), 7.09(2H, d, J=8.7Hz), 7.22(1H, dd, J=7.2 and 4.9Hz), 7.33(1H, d, J=7.8Hz), 7.66-7.70(2H, m), 7.73(1H, dd, J=8.4 and 1.5Hz), 7.78(1H, d, J=8.4Hz), 7.91(1H, d, J=1.2Hz), 8.15-8.19(2H, m), 8.56(1H, d, J=4.6Hz)
IR(KBr) : 1652cm⁻¹
mp : 116.1-119.1°C

[0584] Properties of Compound (256):

³⁵ ¹H-NMR (CDCl₃, δ) : 2.59(3H, s), 4.79(2H, d, J=4.8Hz), 5.46(2H, s), 7.17-7.24(4H, m), 7.35(1H, d, J=7.8Hz), 7.69(2H, dt, J=7.6 and 1.7Hz), 7.83(1H, d, J=8.4Hz), 8.19(2H, d, J=8.6Hz), 8.26(1H, d, J=1.3Hz), 8.57(1H, d, J=4.8Hz)
IR(KBr) : 1634cm⁻¹
mp : 203.7-206.3°C

Examples 195 and 196 (Reference examples)

Synthesis of 2-methyl-1-(2-phenylethyl)-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (257) and 2-methyl-1-(2-phenylethyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (258)

[0585] In the same manner as in Examples 193 and 194, 0.30 g of 2-Methyl-1-(2-phenylethyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (257) and 0.23 g of 2-methyl-1-(2-phenylethyl)-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (258) were formed from 2.00 g of 2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole and 15.0 g of phenetyl iodide.

[0586] Properties of Compound (257):

⁵⁰ ¹H-NMR(CDCl₃, δ) : 2.17(3H, s), 3.10(2H, t, J=6.8Hz), 4.35(2H, t, J=6.8Hz), 4.82(2H, d, J=4.8Hz), 6.92-6.97(2H, m), 7.21-7.28(4H, m), 7.38(1H, d, J=7.8Hz), 7.78(1H, br t), 7.68-7.73(3H, m), 7.98(1H, d, J=0.9Hz), 8.60(1H, dd, J=1.0 and 4.9Hz)
IR(neat) : 1633cm⁻¹
liquid.

[0587] Properties of Compound (258):

¹H-NMR(CDCl₃, δ) : 2.19(3H, s), 3.08(2H, t, J=6.8Hz), 4.35(2H, t, J=6.8Hz), 4.81(2H, d, J=4.8Hz), 6.91-6.96(2H, m), 7.19-7.26(4H, m), 7.31(1H, d, J=8.4Hz), 7.36(1H, d, J=7.8Hz), 7.64-7.73(2H, m), 7.85(1H, dd, J=1.7 and 8.4Hz), 8.19(1H, d, J=1.3Hz), 8.58(1H, d, J=4.0Hz)
IR(neat) : 1643cm⁻¹
liquid.

Examples 197 and 198 (Reference examples)

Synthesis of 1-(2,4-difluorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (259) and 1-(2,4-difluorobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (260)

[0588] In the same manner as in Examples 193 and 194, 0.25 g of 1-(2,4-difluorobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (259) and 0.25 g of 1-(2,4-difluorobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (260) were formed from 1.00 g of 2-methyl-5-[(2-pyridylmethyl) carbamoyl]benzimidazole and 1.00 g of 2,4-difluorobenzyl bromide.

[0589] Properties of Compound (259):

¹H-NMR(CDCl₃, δ) : 2.62(3H, s), 4.78(2H, d, J=4.7Hz), 5.38(2H, s), 6.73-6.79(2H, m), 6.88(1H, t, J=10.0Hz), 7.24 (1H, dd, J=7.3 and 5.1Hz), 7.35(1H, d, J=7.8Hz), 7.67-7.76(4H, m), 7.97(1H, s), 8.58(1H, d, J=4.4Hz).IR(KBr) : 1642cm⁻¹
mp : 98.0-104.0°C

[0590] Properties of Compound (260):

¹H-NMR(CDCl₃, δ) : 2.62(3H, s), 4.79(2H, d, J=4.7Hz), 5.35(2H, s), 6.72-6.81(2H, m), 6.89(1H, t, J=9.8Hz), 7.22 (1H, t, J=6.2Hz), 7.28(1H, d, J=8.4Hz), 7.34(1H, d, J=7.8Hz), 7.63-7.71(2H, m), 7.83(1H, d, J=8.4Hz), 7.97(1H, s), 8.57(1H, d, J=4.7Hz)
IR(KBr) : 1647cm⁻¹
mp : 143.5-144.0°C

Examples 199 and 200 (Reference examples)

Synthesis of 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)-carbamoyl]benzimidazole (261) and 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (262)

[0591] Thirty milliliters of methanol and 0.20 g of 5% palladium on carbon were added to 2.32 g of a mixture of 2-methyl-1-(4-nitrobenzyl)-6-[(2-pyridylmethyl)carbamoyl]benzimidazole and 2-methyl-1-(4-nitrobenzyl)-5-[(2-pyridylmethyl)carbamoyl]-benzimidazole, and the mixture was stirred in a hydrogen atmosphere at room temperature until the starting material disappeared. The solid material was separated through filtration, and the filtrate was concentrated. The resulting residue was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 85:15) to separate 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl] benzimidazole and 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole. Each of these compounds was crystallized from a mixed solvent of chloroform and diethyl ether. The crystals were separated through filtration, and were dried to give 0.354 g of 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole (261) and 0.330 g of 1-(4-aminobenzyl)-2-methyl-5-[(2-pyridylmethyl)carbamoyl]benzimidazole (262).

[0592] Properties of Compound (261):

¹H-NMR(CDCl₃, δ) : 3.00(3H, s), 4.98(2H, s), 5.88(2H, s), 7.55(2H, d, J=8.6Hz), 7.69(2H, d, J=8.6Hz), 7.90(1H, d, J=8.6Hz), 7.96(1H, dt, J=7.1 and 0.6Hz), 8.12(1H, J=8.0Hz), 8.18(1H, dd, J=8.5 and 1.4Hz), 8.55(1H, dt, J=8.0 and 1.7Hz), 8.62(1H, d, J=1.1Hz), 8.77(1H, dd, J=5.9 and 1.1Hz)
IR(KBr) : 1643cm⁻¹
mp : 180.0-181.0°C

[0593] Properties of Compound (262):

¹H-NMR(CDCl₃, δ) : 3.00(3H, s), 5.01(2H, s), 5.83(2H, s), 7.47(2H, d, J=8.5Hz), 7.78(2H, d, J=8.5Hz), 7.78(1H,

d, J=8.9Hz), 7.97(1H, dt, J=7.2 and 0.7Hz), 8.13(1H, J=8.1Hz), 8.15(1H, d, J=8.9Hz), 8.51(1H, s), 8.55(1H, dt, J=7.9 and 1.6Hz), 8.77(1H, d, J=5.8Hz)
 IR(KBr) : 1639, 1612cm⁻¹
 mp : 168.0-171.0°C

5

Example 201 (Reference example)

Synthesis of 1-[4-(benzenesulfonylamino)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (263)

[0594] Triethylamine (0.185 g) and benzenesulfonyl chloride (0.210 g) were added to a solution of 0.340 g of 1-(4-aminobenzyl)-2-methyl-6-[(2-pyridylmethyl)carbamoyl]-benzimidazole in 10 ml of chloroform, and the mixture was stirred at room temperature for 8 hours. Water was added thereto to stop the reaction, and the reaction mixture was extracted with chloroform. The organic layer was washed three times with water, dried, and concentrated. The residue was then purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 100:1 to 4:1) to give 0.300 g of 1-[4-(benzenesulfonylamino)benzyl]-2-methyl-6-[(2-pyridylmethyl)carbamoyl]benzimidazole (263).

[0595] Properties of Compound (263):

¹H-NMR(CDCl₃, δ) : 2.53(3H, s), 4.78(2H, d, J=4.8Hz), 5.28(2H, s), 6.90(2H, t, J=8.6Hz), 6.99(2H, d, J=8.5Hz), 7.11(1H, s), 7.23(1H, dd, J=5.5 and 7.2Hz), 7.34(1H, d, J=7.7Hz), 7.40(2H, t, J=8.1Hz), 7.50(1H, t, J=7.5Hz), 7.66-7.74(6H, m), 7.92(1H, s), 8.56(1H, d, J=4.8Hz)
 IR(KBr) : 1642cm⁻¹
 mp : 204.4-206.5°C

25 Example 202

Synthesis of 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (264)

[0596] To a solution of 0.667 g of benzenesulfonic acid amide in 5 ml of N,N-dimethylformamide were added 0.127 g of 60% sodium hydride at room temperature, and the mixture was stirred for 1 hour. Further, 0.648 g of 1-(2-chlorobenzyl)-6-chloromethyl-2-methylbenzimidazole hydrochloride were added thereto, and the mixture was stirred at room temperature for 18 hours. Water was added to the reaction solution to stop the reaction, and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and was purified through silica-gel column chromatography (eluent: ethyl acetate) to give 0.240 g of 6-benzenesulfonylaminomethyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (264).

[0597] Properties of Compound (264):

¹H-NMR(DMSO-d6, δ) : 2.42(3H, s), 4.02(2H, m), 4.02(2H, m), 5.44(2H, s), 6.36(1H, d, J=7.7Hz), 7.03(1H, d, J=8.4Hz), 7.18(1H, s), 7.21(1H, t), 7.33(1H, t), 7.59-7.43(5H, m), 7.73(2H, d, J=7.5Hz), 8.08(1H, s)
 IR(KBr) : 1522cm⁻¹
 mp : 164.5-167.0°C

Example 203 (Reference example)

45 Synthesis of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)aminomethyl]benzimidazole (265)

[0598] 2-Aminomethylpyridine (0.372 g) was added to a solution of 0.597 g of 1-(biphenyl-4-ylmethyl)-6-chloromethyl-2-methylbenzimidazole and 0.350 g of potassium carbonate in 3 ml of N,N-dimethylformamide, and the mixture was stirred at 60°C for 2 hours. The reaction mixture was extracted with water and with ethyl acetate. The organic layer was washed twice with water, and the solvent was distilled off under reduced pressure. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 9:1), and was recrystallized from a mixed solvent of ethyl acetate and hexane to give 0.300 g of 1-(biphenyl-4-ylmethyl)-2-methyl-6-[(2-pyridylmethyl)aminomethyl]benzimidazole (265).

[0599] Properties of Compound (265):

55 ¹H-NMR(CDCl₃, δ) : 2.57(3H, s), 3.91(2H, s), 3.93(2H, s), 5.35(2H, s), 7.08-7.14(3H, m), 7.23(2H, d, J=7.3Hz), 7.30-7.35(2H, m), 7.41(2H, t), 7.50-7.55(4H, m), 7.57(1H, dt, J=1.8 and 7.6Hz), 7.68(1H, d, J=8.1Hz), 8.53(1H, d, J=4.9Hz)

IR(KBr) : 1618cm⁻¹
 mp : 104.5-106.0°C

Example 204

5 Synthesis of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazole-6-yl]propionamide (266)

[0600] 5% Palladium on carbon (0.500 g) was added to a solution of 0.607 g of N-benzenesulfonyl-1-(2-chlorobenzyl)-2-methylbenzimidazole-6-acrylamide in 150 ml of ethanol, and the mixture was stirred in a hydrogen atmosphere at room temperature for 43 hours. The solid material was separated through filtration, and the filtrate was concentrated. The residue was dissolved in a mixed solution of a 20% potassium hydrogencarbonate aqueous solution and methanol, and was adjusted to a pH of from 5 to 6 with 10% hydrochloric acid. The crystals precipitated were separated through filtration, and was dried to give 0.250 g of N-benzenesulfonyl-3-[1-(2-chlorobenzyl)-2-methylbenzimidazol-6-yl]propionamide (266).

10 [0601] Properties of Compound (266):

¹H-NMR(DMSO-d6, δ) : 2.45(3H, s), 2.52(2H, t), 2.78(2H, t), 5.37(2H, s), 6.88(1H, d, J=8.4Hz), 7.08(2H, d, J=7.4Hz), 7.22-7.34(3H, m), 7.36(1H, t, J=8.1Hz), 7.55(2H, t), 7.67(1H, t), 7.84(2H, d, J=7.6Hz), 12.04(1H, br s)
 IR(KBr) : 1715cm⁻¹
 20 Mass(FAB) : m/e 468(M+1)
 mp : 229.8-233.0°C

Example 205

25 Synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)benzyl]benzimidazole (267)

[0602] In the same manner as in Example 183, 0.279 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(1,2,3-thiadiazol-4-yl)-benzyl]benzimidazole (267) were formed from 0.382 g of N-benzenesulfonyl-4-acetylamino-3-[4-(1,2,3-thiadiazol-4-yl) benzylamino]benzamide.

30 [0603] Properties of Compound (267):

¹H-NMR(DMSO-d6, δ) : 2.56(3H, s), 5.62(2H, s), 7.28(2H, d, J=8.2Hz), 7.58-7.63(3H, m), 7.67(1H, t, J=7.3Hz), 7.74(1H, dd, J=8.5 and 1.2Hz), 7.99(2H, dd, J=8.4 and 1.2Hz), 8.10(2H, d, J=8.2Hz), 8.19(1H, s), 9.58(1H, s), 12.47(1H, s)
 35 IR(KBr) : 1617, 1556cm⁻¹
 mp : 258.5-260.0°C(decomp.)

Example 206

40 Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)benzimidazole sodium salt (268)

[0604] In the same manner as in Example 141, 0.400 g of 1-(2-chlorobenzyl)-2-methyl-6-(8-quinolinesulfonylcarbamoyl)-benzimidazole sodium salt (268) were formed from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.485 g of N,N'-carbonyldiimidazole, 0.625 g of 8-quinolinesulfonamide and 0.457 g of diazabicycloundecene.

45 [0605] Properties of Compound (268):

¹H-NMR(DMSO-d6, δ) : 2.42(3H, s), 5.48(2H, s), 6.32(1H, d, J=7.7Hz), 7.17(1H, t, J=7.5Hz), 7.30(1H, t, J=7.7Hz), 7.42(1H, d, J=8.4Hz), 7.48(1H, dd, J=4.2 and 8.2Hz), 7.53(1H, d, J=8.0Hz), 7.64(1H, t, J=7.7Hz), 7.79(1H, d, J=8.5Hz), 7.88(1H, s), 8.04(1H, d, J=8.1Hz), 8.33-8.37(2H, m), 8.85(1H, dd)
 50 IR(KBr) : 1594cm⁻¹
 Mass(FAB) : m/e 513(M+1)
 mp : 348-352°C (decomp.)

Example 207

55 Synthesis of 6-(4-tert-butylbenzenesulfonylcarbamoyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole sodium salt (269)

[0606] In the same manner as in Example 141, 0.280 g of 6-(4-tert-butylbenzenesulfonylcarbamoyl)-1-(2-chloroben-

zyl)-2-methylbenzimidazole sodium salt (269) were obtained from 0.450 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.486 g of N,N'-carbonyldiimidazole, 0.640 g of 2-tert-butylbenzenesulfonamide and 0.657 g of diazabicycloundecene.

[0607] Properties of Compound (269):

⁵ ¹H-NMR(DMSO-d₆, δ) 1.25(9H, s), 2.46(3H, s), 5.51(2H, s), 6.37(1H, d, J=7.7Hz), 7.18(1H, t), 7.31(1H, t), 7.34(2H, d, J=8.4Hz), 7.44(1H, d, J=8.4Hz), 7.54(1H, d, J=8.0Hz), 7.69(2H, d, J=8.5Hz), 7.78-7.82(2H, m)
 IR(KBr) : 1596cm⁻¹
 Mass(FAB) : m/e 518(M+1)
 mp : 359.5-362°C

Example 208

¹⁵ synthesis of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (270)

[0608] In the same manner as in Production Example 32, 0.30 g of crude N-benzenesulfonyl-4-acetylamino-3-[4-(trifluoromethyl)-benzylamino]benzamide were obtained from 0.50 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide and 0.418 g of 4-(trifluoromethyl)benzyl bromide. When this crude product was dissolved in methanol and was allowed to stand, the crystals were precipitated. The crystals were separated through filtration, and were dried to give 0.160 g of 6-benzenesulfonylcarbamoyl-2-methyl-1-[4-(trifluoromethyl)benzyl]benzimidazole (270).

[0609] Properties of Compound (270):

²⁰ ¹H-NMR(DMSO-d₆, δ) : 2.51(3H, s), 5.66(2H, s), 7.28(2H, d, J=8.1Hz), 7.59-7.65(3H, m), 7.67-7.75(4H, m), 7.99(2H, d, J=7.5Hz), 8.14(1H, d, J=1.0Hz), 12.43(1H, s)
 IR(KBr) : 1618, 1550cm⁻¹
 mp : 278.5-280.0°C

Example 209 (Reference example)

³⁰ Synthesis of 2-benzyl-6-carboxy-1-methylbenzimidazole hydrochloride (271)

[0610] A 5% sodium hydroxide aqueous solution (2.8 g) was added to a solution of 0.340 g of 2-benzyl-6-ethoxycarbonyl-1-methylbenzimidazole in 4 ml of ethanol, and the mixture was heat-refluxed for 1.5 hours. The reaction mixture was acidified with 1-N hydrochloric acid, and was concentrated under reduced pressure. Ethanol was added to the residue to extract the organic substance. Ethanol was distilled off under reduced pressure to give 0.300 g of 2-benzyl-6-carboxy-1-methylbenzimidazole hydrochloride (271).

[0611] Properties of Compound (271):

⁴⁰ ¹H-NMR(DMSO-d₆, δ) : 4.00(3H, s), 4.62(2H, s), 7.33(1H, m), 7.35-7.45(4H, m), 7.83(1H, d, J=8.4Hz), 8.06(1H, d, J=8.4Hz), 8.42(1H, s), 13.3(1H, br s)

Example 210

Synthesis of 5-benzenesulfonylcarbamoyl-2-methylbenzimidazole (272)

[0612] A mixture of 0.500 g of N-benzenesulfonyl-4-acetylamino-3-aminobenzamide, 3.9 g of 35% hydrochloric acid, 15 ml of methanol and 12 ml of water was stirred at 60°C for 1 hour. The reaction mixture was neutralized with a potassium hydrogencarbonate aqueous solution. The crystals precipitated were separated through filtration, and were dried to give 0.404 g of 5-benzenesulfonylcarbamoyl-2-methylbenzimidazole (272).

[0613] Properties of Compound (272):

⁵⁰ ¹H-NMR(DMSO-d₆, δ) : 2.79(3H, s), 7.64-7.68(2H, m), 7.72-7.76(1H, m), 7.81(1H, d, J=8.7Hz), 7.94(1H, dd, J=1.6 and 8.7Hz), 8.02-8.05(2H, m), 8.30(1H, s)
 IR(KBr) : 1701cm⁻¹
 mp : 223.0-227.5°C

Production Example 45

Production of ethyl 3-methoxyacetylamino-4-nitrobenzoate

5 [0614] Ethyl 3-methoxyacetylamino-4-nitrobenzoate (18.7 g) was obtained from 15.0 g of ethyl 3-amino-4-nitrobenzoate and 15.0 g of methoxyacetyl chloride in the same manner as in Production Example 12.

[0615] Properties of the compound:

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.42(3\text{H}, \text{t}, J=7.2\text{Hz}), 3.58(3\text{H}, \text{s}), 4.11(2\text{H}, \text{s}), 4.43(2\text{H}, \text{q}, J=7.2\text{Hz}), 7.85(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.7\text{Hz}), 8.27(1\text{H}, \text{d}, J=8.7\text{Hz}), 9.44(1\text{H}, \text{d}, J=1.6\text{Hz}), 11.15(1\text{H}, \text{s})$

Example 211 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (273)

15 [0616] Crude ethyl 3-[N-(biphenyl-4-ylmethyl)methoxyacetylamino]-4-nitrobenzoate (2.02 g) was obtained from 2.00 g of ethyl 3-methoxyacetylamino-4-nitrobenzoate and 2.98 g of 4-biphenylmethyl bromide in the same manner as in Production Example 14. Subsequently, 1.44 g of crude 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (273) were obtained in the same manner as in Example 24.

Example 212 (Reference example)

Synthesis of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethylbenzimidazole (274)

20 [0617] In the same manner as in Example 53, 0.864 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethylbenzimidazole (274) were formed from 1.44 g of crude 1-(biphenyl-4-ylmethyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

[0618] Properties of Compound (274):

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 3.35(3\text{H}, \text{s}), 4.77(2\text{H}, \text{s}), 5.68(2\text{H}, \text{s}), 7.25(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.61-7.66(4\text{H}, \text{m}), 7.74(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.83(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.5\text{Hz}), 8.08(1\text{H}, \text{d}, J=1.2\text{Hz}), 12.83(1\text{H}, \text{s})$

Example 213

Synthesis of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (275)

35 [0619] In the same manner as in Example 98, 0.429 g of 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (275) were formed from 0.400 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-methoxymethylbenzimidazole, 0.348 g of N,N'-carbonyldiimidazole, 0.294 g of 1-butanesulfonamide and 0.327 g of diazabicycloundecene.

[0620] Properties of Compound (275):

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.84(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.35-1.42(2\text{H}, \text{m}), 1.62-1.70(2\text{H}, \text{m}), 3.33(3\text{H}, \text{s}), 3.51(2\text{H}, \text{t}, J=7.6\text{Hz}), 4.74(2\text{H}, \text{s}), 5.65(2\text{H}, \text{s}), 7.26(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.3\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.62-7.67(4\text{H}, \text{m}), 7.78(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.84(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.24(1\text{H}, \text{d}, J=1.5\text{Hz}), 12.01(1\text{H}, \text{s})$
IR(KBr) : 1684cm⁻¹
mp : 176.0-178.5°C

Example 214 (Reference example)

Synthesis of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (276)

50 [0621] Crude ethyl 3-[N-(4-benzyloxybenzyl)methoxyacetylamino]-4-nitrobenzoate (2.14 g) was obtained from 2.00 g of ethyl 3-methoxyacetylamino-4-nitrobenzoate and 3.30 g of 4-benzyloxybenzyl chloride in the same manner as in Production Example 14. Subsequently, 1.66 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (276) were obtained in the same manner as in Example 24.

Example 215 (Reference example)

Synthesis of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole (277)

5 [0622] In the same manner as in Example 53, 2.64 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole (277) were formed from 3.75 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

[0623] Properties of Compound (277):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 3.34(3\text{H}, \text{s}), 4.74(2\text{H}, \text{s}), 5.05(2\text{H}, \text{s}), 5.53(2\text{H}, \text{s}), 6.97(2\text{H}, \text{d}, J=8.7\text{Hz}), 7.15(2\text{H}, \text{d}, J=8.7\text{Hz}), 7.31(1\text{H}, \text{t}, J=7.2\text{Hz}), 7.41(2\text{H}, \text{d}, J=7.2\text{Hz}), 7.71(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.81(1\text{H}, \text{dd}, J=1.5 \text{ and } 7.4\text{Hz}), 8.04(1\text{H}, \text{d}, J=1.1\text{Hz}), 12.81(1\text{H}, \text{s})$

Example 216

Synthesis of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (278)

15 [0624] In the same manner as in Example 155, 0.321 g of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methoxymethylbenzimidazole (278) were formed from 0.400 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methoxymethylbenzimidazole, 0.322 g of N,N'-carbonyldiimidazole, 0.272 g of 1-butanesulfonamide and 0.302 g of diazabicycloundecene.

[0625] Properties of Compound (278):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.86(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.37-1.44(2\text{H}, \text{m}), 1.65-1.71(2\text{H}, \text{m}), 3.32(3\text{H}, \text{s}), 3.52(2\text{H}, \text{t}, J=7.6\text{Hz}), 4.71(2\text{H}, \text{s}), 5.05(2\text{H}, \text{s}), 5.51(2\text{H}, \text{s}), 6.98(2\text{H}, \text{d}, J=8.7\text{Hz}), 7.15(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.31(1\text{H}, \text{t}, J=7.2\text{Hz}), 7.37(2\text{H}, \text{t}, J=7.2\text{Hz}), 7.41(2\text{H}, \text{d}, J=7.1\text{Hz}), 7.74(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.82(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.21(1\text{H}, \text{s}), 11.98(1\text{H}, \text{s})$
 IR(KBr) : 1685cm⁻¹
 mp : 72.0-74.0°C

Example 217 (Reference example)

Synthesis of 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (279)

25 [0626] Crude ethyl 3-[N-2,4-dichlorobenzyl)methoxyacetylarnino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 3-methoxyacetylarnino-4-nitrobenzoate and 2.08 g of 2,4-dichlorobenzyl chloride in the same manner as in Production Example 14. Subsequently, 3.15 g of crude 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole (279) were obtained in the same manner as in Example 24.

Example 218 (Reference example)

Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (280)

30 [0627] In the same manner as in Example 53, 1.46 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (280) were formed from 3.15 g of crude 1-(2,4-dichlorobenzyl)-6-ethoxycarbonyl-2-methoxymethylbenzimidazole.

[0628] Properties of Compound (280):

35 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 3.23(3\text{H}, \text{s}), 4.70(2\text{H}, \text{s}), 5.68(2\text{H}, \text{s}), 6.54(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.31(1\text{H}, \text{dd}, J=2.2 \text{ and } 8.5\text{Hz}), 7.73(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.76(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.86(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.00(1\text{H}, \text{d}, J=1.1\text{Hz}), 12.85(1\text{H}, \text{s})$

Example 219

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (281)

40 [0629] In the same manner as in Example 98, 0.430 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole (281) were formed from 0.400 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methoxymethylbenzimidazole, 0.355 g of N,N'-carbonyldiimidazole, 0.300 g of 1-butanesulfonamide and 0.333 g of diazabicycloundecene.

decene.

[0630] Properties of Compound (281):

⁵ ¹H-NMR(DMSO-d6, δ) : 0.85(3H, t, J=7.3Hz), 1.37-1.42(2H, m), 1.63-1.69(2H, m), 3.21(3H, s), 3.51(2H, t, J=7.6Hz), 4.68(2H, s), 5.65(2H, s), 6.46(1H, d, J=8.5Hz), 7.31(1H, dd, J=2.0 and 8.4Hz), 7.75(1H, d, J=2.1Hz), 7.80(1H, d, J=8.5Hz), 7.86(1H, dd, J=1.7 and 8.6Hz), 8.14(1H, d, J=1.2Hz), 12.00(1H, s)
IR(KBr) : 1694cm⁻¹
mp : 168.5-170.5°C

¹⁰ Example 220

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)benzimidazole (282)

¹⁵ **[0631]** In the same manner as in Example 98, 0.459 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-propanesulfonylcarbamoyl)-benzimidazole (282) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.328 g of 1-propanesulfonamide and 0.404 g of diazabicycloundecene.

[0632] Properties of Compound (282):

²⁰ ¹H-NMR(DMSO-d6, δ) : 0.98(3H, t, J=7.4Hz), 1.67-1.75(2H, m), 2.50(3H, s), 3.49(2H, t, J=7.7Hz), 5.61(2H, s), 6.45(1H, d, J=7.0Hz), 7.24(1H, dt, J=0.8 and 7.8Hz), 7.35(1H, dt, J=1.4 and 7.4Hz), 7.63(1H, dd, J=0.9 and 7.9Hz), 7.69(1H, d, J=8.5Hz), 7.81(1H, dd, J=1.6 and 8.5Hz), 8.12(1H, d, J=1.6Hz), 11.90(1H, s)
IR(KBr) : 1676cm⁻¹
mp : 217.5-218.5°C

²⁵ Example 221

Synthesis of 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (283)

³⁰ **[0633]** In the same manner as in Example 98, 0.459 g of 6-ethanesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (283) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.290 g of ethanesulfonamide and 0.404 g of diazabicycloundecene.

[0634] Properties of Compound (283):

³⁵ ¹H-NMR(DMSO-d6, δ) : 1.23(3H, t, J=7.3Hz), 2.50(3H, s), 3.50(2H, q, J=7.3Hz), 5.61(2H, s), 6.45(1H, d, J=6.7Hz), 7.24(1H, dt, J=0.9 and 7.5Hz), 7.35(1H, dt, J=1.4 and 7.5Hz), 7.58(1H, dd, J=1.0 and 8.0Hz), 7.69(1H, d, J=8.5Hz), 7.81(1H, dd, J=1.6 and 8.4Hz), 8.13(1H, d, J=1.5Hz), 11.86(1H, s)
IR(KBr) : 1673cm⁻¹
mp : 256.5-258.5°C

⁴⁰ Example 222

Synthesis of 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (284)

⁴⁵ **[0635]** In the same manner as in Example 98, 0.323 g of 6-(propanesultam-1-ylcarbonyl)-1-(2-chlorobenzyl)-2-methylbenzimidazole (284) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.420 g of 1-(3-chloropropane)sulfonamide and 0.404 g of diazabicycloundecene.

[0636] Properties of Compound (284):

⁵⁰ ¹H-NMR(DMSO-d6, δ) : 2.27-2.33(2H, m), 2.52(3H, s), 3.52(2H, t, J=7.0Hz), 3.87(2H, t, J=6.6Hz), 5.59(2H, s), 6.57(1H, d, J=7.7Hz), 7.23(1H, t, J=7.6Hz), 7.34(1H, t, J=6.4Hz), 7.53-7.58(2H, m), 7.67(1H, d, J=8.4Hz), 7.79(1H, d, J=1.1Hz)
IR(KBr) : 1648cm⁻¹
mp : 165.5-166.6°C

Example 223

Synthesis of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole potassium salt (285)

- 5 [0637] In the same manner as in Example 170, 0.196 g of 6-benzenesulfonylcarbamoyl-1-(biphenyl-4-ylmethyl)-2-cyclopropylbenzimidazole potassium salt (285) were obtained from 0.400 g of N-benzenesulfonyl-4-amino-3-(biphenyl-4-ylmethylamino)benzamide and 0.101 g of cyclopropanecarbonyl chloride via N-benzenesulfonyl-3-(biphenyl-4-ylmethylamino)-4-cyclopropanecarbonylaminobenzamide.

[0638] Properties of Compound (285):

- 10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 1.00-1.15(4H, m), 2.23-2.31(1H, m), 5.66(2H, s), 7.21(2H, m, $J=9.1\text{Hz}$), 7.32-7.45(7H, m), 7.59-7.63(4H, m), 7.78-7.83(3H, m), 7.97(1H, s).
 IR(Nujol) : 1540cm⁻¹
 Mass(FAB) : m/e 546(M+1)
 mp : 220.8-224.8°C

Example 224

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (286)

- 20 [0639] In the same manner as in Example 98, 0.491 g of 1-(2-chlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)-benzimidazole (286) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.402 g of 1-pentanesulfonamide and 0.404 g of diazabicycloundecene.

[0640] Properties of Compound (286):

- 25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.81(3H, t, $J=7.2\text{Hz}$), 1.23-1.28(2H, m), 1.32-1.37(2H, m), 1.65-1.69(2H, m), 3.50(2H, t, $J=7.8\text{Hz}$), 5.61(2H, s), 6.45(1H, d, $J=7.5\text{Hz}$), 7.24(1H, t, $J=7.6\text{Hz}$), 7.35(1H, t, $J=7.5\text{Hz}$), 7.57(1H, d, $J=7.9\text{Hz}$), 7.69(1H, d, $J=8.5\text{Hz}$), 7.81(1H, dd, $J=1.7$ and 8.4Hz), 8.12(1H, d, $J=1.2\text{Hz}$), 12.25(1H, s)
 IR(KBr) : 1684cm⁻¹
 mp : 173.3-179.8°C

Example 225

Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[3-methylbutane]-sulfonylcarbamoyl]benzimidazole (287)

- 35 [0641] In the same manner as in Example 98, 0.284 g of 1-(2-chlorobenzyl)-2-methyl-6-[3-methylbutane]-sulfonylcarbamoyl]benzimidazole (287) were formed from 0.300 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.302 g of 1-(3-methyl)butanesulfonamide and 0.303 g of diazabicycloundecene.

[0642] Properties of Compound (287):

- 40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.84(6H, d, $J=6.5\text{Hz}$), 1.52-1.59(2H, m), 1.61-1.70(1H, m), 3.44(2H, t, $J=7.9\text{Hz}$), 5.60(2H, s), 6.45(1H, d, $J=7.8\text{Hz}$), 7.24(1H, t, $J=7.6\text{Hz}$), 7.35(1H, t, $J=7.4\text{Hz}$), 7.57(1H, d, $J=7.9\text{Hz}$), 7.66(1H, d, $J=8.5\text{Hz}$), 7.81(1H, dd, $J=1.6$ and 8.6Hz), 8.09(1H, s), 11.87(1H, s)
 IR(KBr) : 1682cm⁻¹
 mp : 201.0-204.1°C

Example 226

Synthesis of 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole (288)

- 50 [0643] In the same manner as in Example 98, 0.379 g of 1-(2-chlorobenzyl)-6-(1-hexanesulfonylcarbamoyl)-2-methylbenzimidazole (288) were formed from 0.300 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.335 g of 1-hexanesulfonamide and 0.303 g of diazabicycloundecene.

[0644] Properties of Compound (288):

- 55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.81(3H, t, $J=7.0\text{Hz}$), 1.18-1.28(4H, m), 1.32-1.41(2H, m), 1.63-1.71(2H, m), 2.53(3H, s), 3.50(2H, t, $J=7.7\text{Hz}$), 5.64(2H, s), 6.51(1H, d, $J=7.7\text{Hz}$), 7.25(1H, dt, $J=1.2$ and 7.8Hz), 7.36(1H, dt, $J=1.4$ and 7.7Hz), 7.58(1H, dd, $J=1.0$ and 8.0Hz), 7.72(1H, d, $J=8.5\text{Hz}$), 7.84(1H, dd, $J=1.6$ and 8.5Hz), 8.15(1H, d, $J=1.3\text{Hz}$),

11.87(1H, s)
 IR(KBr) : 1682cm⁻¹
 mp : 141.2-143.5°C

5 Example 227 (Reference example)

Synthesis of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole (289)

10 [0645] In the same manner as in Example 18, 0.760 g of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole (289) were formed from 1.01 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1 ml of diphenylphosphorylazide, 1 ml of diisopropylethylamine and 25 ml of tert-butyl alcohol.

[0646] Properties of Compound (289):

15 ¹H-NMR(CDCl₃, δ) : 1.49(9H, s), 2.47(3H, s), 5.37(2H, s), 6.41(1H, d, J=7.5Hz), 6.55(1H, br s), 6.93(1H, dd, J=1.9 and 8.6Hz), 7.08(1H, t, J=7.5Hz), 7.22(1H, t), 7.44(1H, d, J=8.0Hz), 7.62(2H, d, J=8.6Hz)

Example 228 (Reference example)

Synthesis of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole (290)

20 [0647] In the same manner as in Example 22, 0.420 g of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole (290) were formed from 0.760 g of 6-tert-butoxycarbonylamino-1-(2-chlorobenzyl)-2-methylbenzimidazole.

[0648] Properties of Compound (290):

25 ¹H-NMR(DMSO-d6, δ) : 2.37(3H, s), 4.83(2H, br s), 5.32(2H, s), 6.33(1H, d, J=1.9Hz), 6.42(1H, d, J=7.7Hz), 6.46(1H, dd, J=1.9 and 8.5Hz), 7.19-7.24(2H, m), 7.31(1H, t), 7.53(1H, d, J=7.9Hz)

Example 229

30 Synthesis of 6-(1-butanesulfonylamino)-1-(2-chlorobenzyl)-2-methylbenzimidazole (291)

35 [0649] In the same manner as in Example 20, 0.230 g of 6-(1-butanesulfonylamino)-1-(2-chlorobenzyl)-2-methylbenzimidazole (291) were formed from 0.300 g of 6-amino-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.216 g of 1-butanethionyl chloride and 0.130 g of triethylamine.

[0650] Properties of Compound (291):

40 ¹H-NMR(DMSO-d6, δ) : 0.74(3H, m), 1.23(2H, m), 1.55(2H, m), 2.50(3H, s), 2.89(2H, m), 5.47(2H, s), 6.58(1H, d, J=7.4Hz), 7.02(1H, d, J=8.5Hz), 7.10(1H, s), 7.23(1H, t), 7.33(1H, t), 7.52(2H, m), 9.55(1H, s)
 IR(KBr) : 1629cm⁻¹
 mp : 149.5-151.0°C

Production Example 46

45 Production of methyl 2-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate

[0651] In the same manner as in Production Example 14, 0.250 g of methyl 2-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate were formed from 1.00 g of methyl 2-acetylamino-3-nitrobenzoate and 0.985 g of 2,4-dichlorobenzyl chloride.

[0652] Properties of the compound:

50 ¹H-NMR(CDCl₃, δ) : 1.99(3H, s), 3.71(3H, s), 4.85(1H, d, J=4.5Hz), 4.98(1H, d, J=4.5Hz), 7.17-7.22(2H, m), 7.46(1H, d, J=7.9Hz), 7.63(1H, t, J=7.9Hz), 7.98(1H, d, J=8.0Hz), 8.09(1H, d, J=7.9Hz)

Example 230 (Reference example)

55 Synthesis of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole (292)

[0653] In the same manner as in Example 24, 5.15 g of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimi-

dazole (292) were formed from 6.50 g of methyl 2-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate.

[0654] Properties of Compound (292):

⁵ ¹H-NMR(CDCl₃, δ) : 2.53(3H, s), 3.70(3H, s), 5.72(2H, s), 6.26(1H, d, J=8.4Hz), 7.04(1H, dd, J=2.0 and 8.4Hz), 7.28(1H, t, J=7.9Hz), 7.45(1H, d, J=2.0Hz), 7.75(1H, d, J=7.8Hz), 7.93(1H, d, J=7.9Hz)

Example 231 (Reference example)

¹⁰ Synthesis of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (293)

[0655] In the same manner as in Example 53, 1.76 g of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (293) were formed from 2.00 g of 1-(2,4-dichlorobenzyl)-7-ethoxycarbonyl-2-methylbenzimidazole.

[0656] Properties of Compound (293):

¹⁵ ¹H-NMR(DMSO-d6, δ) : 2.49(3H, s), 5.81(2H, s), 6.09(1H, d, J=8.4Hz), 7.21-7.28(2H, m), 7.62(1H, d, J=7.8Hz), 7.67(1H, d, J=2.2Hz), 7.83(1H, d, J=8.0Hz), 13.04(13, br s)

Example 232

²⁰ Synthesis of 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (294)

[0657] In the same manner as in Example 98, 0.325 g of 7-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (294) were formed from 0.463 g of 7-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.448 g of N,N'-carbonyldiimidazole, 0.379 g of 1-butanesulfonamide and 0.421 g of diazabicycloundecene.

²⁵ [0658] Properties of Compound (294):

¹H-NMR(DMSO-d6, δ) : 0.84(3H, t, J=7.3Hz), 1.33(2H, m), 1.44(2H, m), 2.53(3H, s), 3.16(2H, m), 5.64(2H, s), 6.03(1H, d, J=8.4Hz), 7.25(1H, dd, J=2.1 and 8.4Hz), 7.30(1H, t, J=7.8Hz), 7.44(1H, d, J=7.4Hz), 7.68(1H, d, J=2.1Hz), 7.87(1H, d, J=7.8Hz), 12.18(1H, br s)

³⁰ IR(KBr) : 1690cm⁻¹

mp : 98.5-102.0°C

Example 233

³⁵ Synthesis of 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl)propane]sulfonylcarbamoyl]benzimidazole (295)

[0659] In the same manner as in Example 149, 0.604 g of 1-(2-chlorobenzyl)-2-methyl-6-[1-[3-(trimethylsilyl)propane]sulfonylcarbamoyl]benzimidazole (295) were formed from 0.400 g of 6-carboxy-1-(2-chlorobenzyl)-2-methylbenzimidazole, 0.431 g of N,N'-carbonyldiimidazole, 0.520 g of 1-[3-(trimethylsilyl)propane]sulfonamide and 0.404 g of diazabicycloundecene.

⁴⁰ [0660] Properties of Compound (295):

¹H-NMR(DMSO-d6, δ) : -0.06(9H, s), 0.61(2H, t, J=8.6Hz), 1.66-1.73(2H, m), 2.50(3H, s), 3.51(2H, t, J=7.7Hz), 5.61(2H, s), 6.46(1H, d, J=7.8Hz), 7.24(1H, t, J=7.6Hz), 7.35(1H, t, J=7.6Hz), 7.57(1H, dd, J=7.9 and 0.9Hz), 7.70(1H, d, J=8.5Hz), 7.81(1H, dd, J=1.5 and 8.5Hz), 8.12(1H, d, J=1.4Hz), 11.98(1H, s)

⁴⁵ IR(KBr) : 1688cm⁻¹

mp : 197.0-203.9°C

Example 234 (Reference example)

⁵⁰ Synthesis of 4-ethoxycarbonyl-2-methylbenzimidazole (296)

[0661] A mixture of 8.03 g of methyl 2-acetylamino-3-nitrobenzoate, 18.8 g of reduced iron, 20 ml of acetic acid and 40 ml of ethanol was heat-refluxed for 18 hours. After the solvent was concentrated, chloroform and 10% hydrochloric acid were added to the residue for extraction. The aqueous layer was alkalized with a saturated aqueous solution of sodium hydrogencarbonate, and was extracted with chloroform. Chloroform was then distilled off under reduced pressure to give 1.61 g of 4-ethoxycarbonyl-2-methylbenzimidazole (296).

⁵⁵ [0662] Properties of Compound (296):

¹H-NMR(CDCl₃, δ) : 1.43(3H, t), 2.66(3H, s), 4.45(2H, q), 7.24-7.28(1H, m), 7.84-7.89(2H, m), 10.26(1H, br s)

Example 235 (Reference example)

5 Synthesis of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole (297)

[0663] A mixture of 1.61 g of 4-ethoxycarbonyl-2-methylbenzimidazole, 3.08 g of 2,4-dichlorobenzyl chloride, 1.51 g of potassium iodide, 1.05 g of potassium carbonate and 4 ml of N,N-dimethylformamide was stirred at 80°C for 16 hours. The reaction mixture was extracted with chloroform and with water. The chloroform layer was washed with water, dried, and concentrated. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:8) to give 0.730 g of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole (297).

[0664] Properties of Compound (297):

15 ¹H-NMR(CDCl₃, δ) : 1.47(3H, t, J=7.1Hz), 2.63(3H, s), 4.52(2H, q, J=7.1Hz), 5.39(2H, s), 6.30(1H, d, J=8.4Hz), 7.06(1H, dd, J=2.1 and 8.4Hz), 7.25(1H, t, J=7.9Hz), 7.32(1H, dd, J=1.0 and 7.9Hz), 7.48(1H, d, J=2.0Hz), 7.93(1H, dd, J=1.0 and 7.7Hz)

Example 236 (Reference example)

20 Synthesis of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (298)

[0665] In the same manner as in Example 53, 0.575 g of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (298) were formed from 0.730 g of 1-(2,4-dichlorobenzyl)-4-ethoxycarbonyl-2-methylbenzimidazole.

25 [0666] Properties of Compound (298):

¹H-NMR(DMSO-d6, δ) : 2.65(3H, s), 5.67(2H, s), 6.73(1H, d, J=8.3Hz), 7.33(1H, dd, J=2.2 and 8.4Hz), 7.39(1H, t, J=7.9Hz), 7.74(1H, d, J=2.2Hz), 7.76(1H, d, J=8.2Hz), 7.85(1H, d, J=7.5Hz)

30 Example 237

Synthesis of 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (299)

[0667] In the same manner as in Example 98, 0.275 g of 4-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (299) were formed from 0.350 g of 4-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.339 g of N,N'-carbonyldiimidazole, 0.287 g of 1-butanesulfonamide and 0.318 g of diazabicycloundecene.

[0668] Properties of Compound (299):

40 ¹H-NMR(DMSO-d6, δ) : 0.86(3H, t, J=7.3Hz), 1.42(2H, m), 1.73(2H, m), 2.61(3H, s), 3.61(2H, m), 5.65(2H, s), 6.67(1H, d, J=8.4Hz), 7.32(1H, dd, J=2.1 and 8.4Hz), 7.39(1H, t, J=7.9Hz), 7.73(1H, d, J=2.1Hz), 7.78(1H, d, J=8.0Hz), 7.91(1H, d, J=7.7Hz), 12.66(1H, br s)

IR(KBr) : 1699cm⁻¹

mp : 180.7-183.6°C

45 Example 238 (Reference example)

Synthesis of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (300)

50 [0669] In the same manner as in Production Example 14, crude ethyl 3-[N-(4-benzyloxybenzyl)acetylamino]-4-nitrobenzoate was obtained from 2.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 3.69 g of 4-benzyloxybenzyl chloride. Subsequently, 4.09 g of crude 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (300) were formed in the same manner as in Example 24.

Example 239 (Reference example)

55 Synthesis of 1-(4-benzyloxybenzyl)-6-carboxy-2-methylbenzimidazole (301)

[0670] In the same manner as in Example 53, 1.13 g of 1-(4-benzyloxybenzyl)-6-carboxy-2-methylbenzimidazole

(301) were formed from 4.09 g of 1-(4-benzyloxybenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole.

[0671] Properties of Compound (301):

5 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.57(3H, s), 5.05(2H, s), 5.48(2H, s), 6.97(2H, d, $J=8.6\text{Hz}$), 7.08(2H, d, $J=8.5\text{Hz}$),
 7.28-7.43(5H, m), 7.60(1H, d, $J=8.3\text{Hz}$), 7.78(1H, d, $J=7.5\text{Hz}$), 8.07(1H, s), 12.72(1H, s)

Example 240

Synthesis of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (302)

10 **[0672]** In the same manner as in Example 149, 0.206 g of 1-(4-benzyloxybenzyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (302) were formed from 0.300 g of 6-carboxy-1-(4-benzyloxybenzyl)-2-methylbenzimidazole, 0.242 g of N,N'-carbonyldiimidazole, 0.204 g of 1-butanesulfonamide and 0.227 g of diazabicycloundecene.

15 **[0673]** Properties of Compound (302):

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.87(3H, t, $J=7.3\text{Hz}$), 1.38-1.43(2H, m), 1.64-1.71(2H, m), 2.54(3H, s), 3.49(2H, t, $J=6.8\text{Hz}$), 5.05(2H, s), 5.45(2H, s), 6.98(2H, d, $J=8.7\text{Hz}$), 7.10(2H, d, $J=8.7\text{Hz}$), 7.31(1H, t, $J=7.2\text{Hz}$), 7.37(2H, t, $J=7.2\text{Hz}$), 7.41(2H, d, $J=7.3\text{Hz}$), 7.62(1H, d, $J=8.5\text{Hz}$), 7.79(1H, dd, $J=1.5$ and 8.4Hz), 8.23(1H, s), 11.93(1H, s)
 20 IR(KBr) : 1684 cm⁻¹
 mp : 132.4-137.7°C

Example 241 (Reference example)

Synthesis of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (303)

25 **[0674]** In the same manner as in Production Example 14, 0.750 g of crude ethyl 3-[N-[(2'-cyanobiphenyl-4-yl)methyl]acetylamino]-4-nitrobenzoate were obtained from 1.00 g of ethyl 3-acetylamino-4-nitrobenzoate and 1.30 g of 4'-bromomethyl-2-cyanobiphenyl. Subsequently, 0.410 g of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (303) were formed in the same manner as in Example 24.

30 **[0675]** Properties of Compound (303):

15 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 1.40(3H, t), 2.63(3H, s), 4.39(2H, q), 5.46(2H, s), 7.17(2H, d), 7.40-7.66(5H, m), 7.73-7.78(2H, m), 8.00(1H, dd, $J=1.5$ and 8.5Hz), 8.05(1H, d, $J=1.2\text{Hz}$)

Example 242 (Reference example)

Synthesis of 6-carboxy-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (304)

40 **[0676]** In the same manner as in Example 53, 0.190 g of 6-carboxy-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (304) were formed from 0.410 g of 6-ethoxycarbonyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

45 **[0677]** Properties of Compound (304):

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.59(3H, s), 5.67(2H, s), 7.24(2H, d, $J=8.1\text{Hz}$), 7.53-7.64(5H, m), 7.75(1H, t, $J=7.7\text{Hz}$),
 7.80(1H, d), 7.92(1H, d, $J=7.7\text{Hz}$), 8.12(1H, s), 12.74(1H, br s)

Example 243

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (305)

50 **[0678]** In the same manner as in Example 155, 0.155 g of 6-(1-butanesulfonylcarbamoyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methylbenzimidazole (305) were formed from 0.187 g of 6-carboxy-1-[(2'-biphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.160 g of N,N'-carbonyldiimidazole, 0.135 g of 1-butanesulfonamide and 0.150 g of diazabicycloundecene by being purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 20:1).

55 **[0679]** Properties of Compound (305):

15 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.83(3H, t, $J=7.4\text{Bz}$), 1.34(2H, m), 1.60(2H, m), 2.56(3H, s), 3.27(2H, m), 5.62(2H, s), 7.23

(2H, d, J=8.2Hz), 7.53-7.57(4H, m), 7.60(1H, d, J=7.8Hz), 7.75(1H, dt, J=1.0 and 7.8Hz), 7.83(1H, dd, J=1.5 and 8.4Hz), 7.92(1H, d), 8.13(1H, s), 11.92(1H, br s).
 IR(KBr) : 2223cm⁻¹.
 mp : 115-118°C

5

Production Example 47

Production of 2-fluoro-4'-methylbiphenyl

[0680] Thirty milliliters of a 1.6-M-n-butyllithium hexane solution and a solution of 8.33 g of 4-bromotoluene in 30 ml of tetrahydrofuran were added in this order to 30 ml of tetrahydrofuran which had been cooled to -78°C in a nitrogen atmosphere, and the mixture was then stirred at -78°C for 1 hour. A solution containing 6.64 g of zinc chloride which had been dehydrated through heat-melting under reduced pressure in 30 ml of tetrahydrofuran was added thereto at -78°C, and the mixture was stirred at room temperature for 1 hour. This solution was added to a solution of 7.22 g of 2-fluoroiodobenzene and 0.52 g of tetrakis(trifluorophosphine)palladium (O) in 30 ml of tetrahydrofuran at room temperature, and the mixed solution was stirred for 24 hours. The reaction solution was diluted with 300 ml of ethyl acetate, and the dilute solution was extracted with the addition of 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried, and then concentrated. The residue was purified through silica-gel column chromatography (eluent: hexane) to give 6.05 g of oily 2-fluoro-4'-methylbiphenyl.

[0681] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 2.39(3H, s), 7.10-7.30(5H, m), 7.39-7.49(3H, m)

Production Example 48

Production of 2-fluoro-4'-bromomethylbiphenyl

[0682] A mixture of 8.70 g of 2-fluoro-4'-methylbiphenyl, 8.32 g of N-bromosuccinimide, 0.10 g of 2,2'-azobisisobutyronitrile and 150 ml of carbon tetrachloride was heat-refluxed for 5 hours. The reaction solution was washed with water, and the organic layer was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 9:1) to obtain crude 2-fluoro-4'-bromomethylbiphenyl. Further, this compound was crystallized from hexane to give 4.93 g of 2-fluoro-4'-bromomethylbiphenyl.

[0683] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 4.55(2H, s), 7.13-7.23(2H, m), 7.33(1H, m), 7.43(1H, m), 7.47(2H, d, J=8.1Hz), 7.54(2H, d, J=8.1Hz)

Production Example 49

Production of ethyl 3-[N-[2'-fluorobiphenyl-4-yl)methyl]-acetylamino]-4-nitrobenzoate

[0684] Ethyl 3-[N-[2'-fluorobiphenyl-4-yl)methyl]acetylamino]-4-nitrobenzoate (1.90 g) was formed from 1.54 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.26 g of 2-fluoro-4'-bromomethylbiphenyl in the same manner as in Production Example 14.

[0685] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 1.33(3H, t, J=7.1Hz), 1.92(3H, s), 4.36(2H, m), 4.44(1H, d, J=4.4Hz), 5.32(1H, d, J=4.4Hz), 7.13(1H, m), 7.18-7.22(3H, m), 7.31(1H, m), 7.40(1H, dt, J=1.6 and 7.7Hz), 7.44(2H, d), 7.67(1H, d, J=1.6Hz), 7.94(1H, d, J=8.4Hz), 8.15(1H, dd, J=1.8 and 8.4Hz)

50

Example 244 (Reference example)

Synthesis of 6-ethoxycarbonyl-1-[2'-fluorobiphenyl-4-yl)-methyl]-2-methylbenzimidazole (306)

[0686] In the same manner as in Example 24, 1.53 g of 6-ethoxycarbonyl-1-[2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (306) were formed from 1.90 g of ethyl 3-[N-[2'-fluorobiphenyl-4-yl)methyl]acetylamino]-4-nitrobenzoate.

[0687] Properties of Compound (306):

¹H-NMR(CDCl₃, δ) : 1.40(3H, t, J=7.1Hz), 2.62(3H, s), 4.38(2H, q, J=7.1Hz), 5.43(2H, s), 7.10-7.17(3H, m), 7.19(1H, dt, J=1.0 and 7.5Hz), 7.31(1H, m), 7.38(1H, dt, J=1.8 and 7.8Hz), 7.50(2H, dd), 7.74(1H, d, J=8.5Hz), 8.00(1H, dd, J=1.4 and 8.4Hz), 8.06(1H, s)

5 Example 245 (Reference example)

Synthesis of 6-carboxy-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (307)

10 [0688] In the same manner as in Example 53, 1.24 g of 6-carboxy-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (307) were formed from 1.50 g of 6-ethoxycarbonyl-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

[0689] Properties of Compound (307):

15 ¹H-NMR(DMSO-d6, δ) : 2.59(3H, s), 5.63(2H, s), 7.19(2H, d, J=8.1Hz), 7.24-7.31(2H, m), 7.39(1H, m), 7.46-7.53(3H, m), 7.62(1H, d, J=8.4Hz), 7.80(1H, dd, J=1.3 and 8.4Hz), 8.10(1H, s)

Example 246

20 Synthesis of 6-(1-ethanesulfonylcarbamoyl)-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (308)

25 [0690] In the same manner as in Example 98, 0.340 g of 6-(1-ethanesulfonylcarbamoyl)-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (308) were formed from 0.455 g of 6-carboxy-1-[(2'-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.409 g of N,N'-carbonyldiimidazole, 0.346 g of 1-butanesulfonamide and 0.384 g of diazabicycloundecene.

25 [0691] Properties of Compound (308):

30 ¹H-NMR(DMSO-d6, δ) : 0.84(3H, t, J=7.3Hz), 1.39(1H, m), 1.67(1H, m), 2.57(3H, s), 3.51(1H, t), 5.60(2H, s), 7.21(2H, d, J=8.0Hz), 7.24-7.30(2H, m), 7.39(1H, m), 7.48(1H, t), 7.52(2H, d, J=8.0Hz), 7.66(1H, d, J=8.5Hz), 7.80(1H, d, J=8.5Hz), 8.25(1H, s), 11.93(1H, br s)

30 Production Example 50

Production of 3-fluoro-4-methylbiphenyl

35 [0692] Thirty milliliters of a 1.6-M-n-butyllithium hexane solution and a solution of 9.21 g of 4-bromo-2-fluorotoluene in 30 ml of tetrahydrofuran were added in this order to 30 ml of tetrahydrofuran which had been cooled to -78°C in a nitrogen atmosphere, and the mixture was then stirred at -78°C for 1 hour. A solution containing 6.64 g of zinc chloride which had been dehydrated through heat-melting under reduced pressure in 30 ml of tetrahydrofuran was added thereto at -78°C, and the mixture was stirred at room temperature for 1 hour. The reaction solution was added to a solution of 6.63 g of iodobenzene and 0.52 g of tetrakis(triphenylphosphine)palladium (0) in 30 ml of tetrahydrofuran at room temperature, and the mixed solution was stirred for 24 hours. The reaction solution was diluted with 300 ml of ethyl acetate, and the dilute solution was extracted with the addition of 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried, and then concentrated. The residue was purified through silica-gel column chromatography (eluent: hexane) to give 6.00 g of oily 3-fluoro-4-methylbiphenyl.

45 [0693] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 2.31(3H, d, J=1.8Hz), 7.20-7.28(3H, m), 7.34(1H, m), 7.43(2H, t), 7.55(2H, d)

50 Production Example 51

Production of 4-bromomethyl-3-fluorobiphenyl

55 [0694] A mixture of 6.00 g of 3-fluoro-4-methylbiphenyl, 5.73 g of N-bromosuccinimide, 0.075 g of 2,2'-azobisisobutyronitrile and 120 ml of carbon tetrachloride was heat-refluxed for 5 hours. The reaction solution was washed with water, and the organic layer was concentrated. The resulting residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 9:1) to give 8.30 g of oily 4-bromomethyl-3-fluorobiphenyl.

[0695] Properties of the compound:

¹H-NMR(CDCl₃, δ) : 4.57(2H, s), 7.30(1H, d, J=11.0Hz), 7.34-7.40(2H, m), 7.45(3H, m), 7.56(2H, d)

Production Example 52

5 Production of ethyl 3-[N-[(3-fluorobiphenyl-4-yl)methyl]-acetylamino]-4-nitrobenzoate

[0696] In the same manner as in Production Example 14, 2.68 g of crude ethyl 3-[N-[(3-fluorobiphenyl-4-yl)methyl]-acetylamino]-4-nitrobenzoate were obtained from 1.54 g of ethyl 3-acetylamino-4-nitrobenzoate and 2.26 g of 3-fluoro-4-bromomethylbiphenyl.

10 Example 247 (Reference example)

Synthesis of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (309)

15 [0697] In the same manner as in Example 24, 1.34 g of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (309) were formed from 2.68 g of crude ethyl 3-[N-[(3-fluorobiphenyl-4-yl)methyl]-acetylamino]-4-nitrobenzoate.

[0698] Properties of Compound (309):

20 ¹H-NMR(CDCl₃, δ) : 1.40(3H, t, J=7.1Hz), 2.65(3H, s), 4.39(2H, q, J=7.1Hz), 5.46(2H, s), 6.79(1H, t, J=8.0Hz), 7.25(1H, m), 7.34-7.40(2H, m), 7.41-7.47(2H, m), 7.50-7.54(2H, m), 7.74(1H, d, J=8.5Hz), 7.99(1H, dd, J=1.5 and 8.4Hz), 8.07(1H, d, J=1.3Hz)

25 Example 248 (Reference example)

Synthesis of 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (310)

30 [0699] In the same manner as in Example 53, 1.15 g of 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (310) were formed from 1.34 g of 6-ethoxycarbonyl-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole.

[0700] Properties of Compound (310):

35 ¹H-NMR(DMSO-d6, δ) : 2.59(3H, s), 5.64(2H, s), 7.03(1H, t, J=8.0Hz), 7.37(1H, t, J=7.3Hz), 7.42-7.48(3H, m), 7.56-7.68(4H, m), 7.79(1H, dd, J=1.4 and 8.4Hz), 8.11(1H, s), 12.7(1H, br s)

40 Example 249

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (311)

45 [0701] In the same manner as in Example 98, 0.236 g of 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole (311) were formed from 0.390 g of 6-carboxy-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 0.351 g of N,N'-carbonyldiimidazole, 0.297 g of 1-butanesulfonamide and 0.329 g of diazabicycloundecene.

[0702] Properties of Compound (311):

50 ¹H-NMR(DMSO-d6, δ) : 0.84(3H, t), 1.38(2H, m), 1.65(2H, m), 2.57(3H, s), 3.48(2H, m), 5.63(2H, s), 6.93(1H, t, J=8.1Hz), 7.37(1H, m), 7.42-7.47(3H, m), 7.60(1H, dd, J=1.7 and 11.8Hz), 7.62-7.68(3H, m), 7.80(1H, dd, J=1.5 and 8.4Hz), 8.21(1H, d, J=1.3Hz), 11.90(1H, br s).

IR(Nujol) : 1681cm⁻¹

mp : 227-230°C

55 Example 250

Synthesis of 1-(2-chlorobenzyl)-6-[(2-methoxyethane)sulfonylcarbamoyl]-2-methylbenzimidazole (312)

[0703] In the same manner as in Example 98, 0.149 g of 1-(2-chlorobenzyl)-6-[(2-methoxyethane)sulfonylcarbamoyl]-2-methylbenzimidazole (312) were formed from 0.300 g of 1-(biphenyl-4-ylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.258 g of (2-ethoxyethane)sulfonamide and 0.256 g of diazabicycloundecene.

decene.

[0704] Properties of Compound (312):

⁵ ¹H-NMR(DMSO-d₆, δ) : 0.87(3H, t, J=6.9Hz), 1.30(3H, t, J=8.0Hz), 2.89(2H, q, J=7.6Hz), 3.25-3.35(28, m), 3.63-3.74(2H, m), 5.59(2H, s), 7.17(2H, d, J=8.1Hz), 7.34(1H, t, J=7.0Hz), 7.44(2H, t, J=7.6Hz), 7.58-7.68(5H, m), 7.82(1H, d, J=8.4Hz), 8.23(1H, s), 11.88(1H, s).
IR(Nujol) : 1681cm⁻¹.
mp : 78-81°C

¹⁰ Example 251

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (313)

¹⁵ **[0705]** In the same manner as in Example 98, 0.196 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)-benzimidazole (313) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.323 g of N,N'-carbonyldiimidazole, 0.301 g of 1-pentanesulfonamide and 0.303 g of diazabicycloundecene.

[0706] Properties of Compound (313):

²⁰ ¹H-NMR(DMSO-d₆, δ) : 0.81(3H, t, J=7.3Hz), 1.22-1.30(2H, m), 1.32-1.39(2H, m), 1.64-1.71(2H, m), 2.50(3H, s), 3.50(2H, t, J=7.8Hz), 5.59(2H, s), 6.45(1H, d, J=8.4Hz), 7.33(1H, dd, J=2.2 and 8.5Hz), 7.69(1H, d, J=8.5Hz), 7.76(1H, d, J=2.1Hz), 7.80(1H, dd, J=1.6 and 8.5Hz), 8.10(1H, s), 11.89(1H, s).
IR(Nujol) : 1682cm⁻¹.
mp : 213.2-214.6°C

²⁵ Example 252

Synthesis of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]sulfonylcarbamoyl]benzimidazole (314)

³⁰ **[0707]** In the same manner as in Example 98, 0.178 g of 1-(biphenyl-4-ylmethyl)-2-ethyl-6-[1-[3-(methylthio)propane]-sulfonylcarbamoyl]benzimidazole (314) were formed from 0.300 g of 6-carboxy-1-(biphenyl-4-ylmethyl)-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.285 g of 1-[(3-methylthio)propane]sulfonamide and 0.256 g of diazabicycloundecene.

[0708] Properties of Compound (314):

³⁵ ¹H-NMR(DMSO-d₆, δ) : 1.30(3H, t, J=7.5Hz), 1.91-1.99(2H, m), 1.97(3H, s), 2.58(2H, t, J=7.2Hz), 2.90(2H, q, J=7.6Hz), 3.55-3.61(2H, m), 5.60(2H, s), 7.18(2H, d, J=8.2Hz), 7.35(1H, t, J=7.3Hz), 7.44(2H, t, J=7.5Hz), 7.60-7.66(4H, m), 7.69(1H, d, J=8.5Hz), 7.82(1H, dd, J=1.8 and 8.5Hz), 8.24(1H, s), 11.98(1H, s).
IR(Nujol) : 1671cm⁻¹.
mp : 89.9-91.2°C

⁴⁰ Example 253

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole (315)

⁴⁵ **[0709]** In the same manner as in Example 98, 0.258 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)-benzimidazole (315) were formed from 0.300 g of 6-carboxy-1-(4-biphenylmethyl)-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.254 g of 1-pentanesulfonamide and 0.256 g of diazabicycloundecene.

[0710] Properties of Compound (315):

⁵⁰ ¹H-NMR(DMSO-d₆, δ) : 0.87(3H, t, J=7.2Hz), 1.22-1.39(4H, m), 1.30(3H, t, J=7.5Hz), 1.66-1.73(2H, m), 2.90(2H, q, J=7.4Hz), 3.51(2H, t, J=7.7Hz), 5.60(2H, s), 7.18(2H, d, J=8.2Hz), 7.34(1H, t, J=7.4Hz), 7.44(2H, t, J=7.6Hz), 7.60-7.67(4H, m), 7.71(1H, d, J=8.4Hz), 7.81(1H, dd, J=1.6 and 8.4Hz), 8.27(1H, d, J=1.1Hz), 11.92(1H, s).
IR(Nujol) : 1682cm⁻¹.
mp : 175.3-178.4°C

⁵⁵

Example 254

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dicyclobenzyl)-2-ethylbenzimidazole (316)

5 [0711] In the same manner as in Example 98, 0.253 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dicyclobenzyl)-2-ethylbenzimidazole (316) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole, 0.258 g of N,N'-carbonyldiimidazole, 0.217 g of 1-butanesulfonamide and 0.262 g of diazabicycloundecene.

[0712] Properties of Compound (316):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.85(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.27(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.35-1.43(2\text{H}, \text{m}), 1.63-1.70(2\text{H}, \text{m}), 2.81(2\text{H}, \text{q}, J=7.4\text{Hz}), 3.51(2\text{H}, \text{t}, J=7.7\text{Hz}), 5.59(2\text{H}, \text{s}), 6.41(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.32(1\text{H}, \text{dd}, J=2.0 \text{ and } 8.4\text{Hz}), 7.73(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.76(1\text{H}, \text{d}, J=2.0\text{Hz}), 7.81(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.12(1\text{H}, \text{d}, J=1.6\text{Hz}), 11.87(1\text{H}, \text{s})$.
IR(Nujol) : 1694 cm⁻¹.
mp : 175.7-176.9°C

15

Example 255

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]benzimidazole (317)

20 [0713] In the same manner as in Example 98, 0.273 g of 1-(4-biphenylmethyl)-2-ethyl-6-[1-(3-methyl)butanesulfonylcarbamoyl]benzimidazole (317) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.254 g of 1-(3-methyl)butanesulfonamide and 0.256 g of diazabicycloundecene.

[0714] Properties of Compound (317):

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.85(6\text{H}, \text{d}, J=6.5\text{Hz}), 1.30(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.55-1.62(2\text{H}, \text{m}), 1.63-1.70(1\text{H}, \text{m}), 2.90(2\text{H}, \text{q}, J=7.4\text{Hz}), 3.52(2\text{H}, \text{t}, J=7.9\text{Hz}), 5.61(2\text{H}, \text{s}), 7.19(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.61-7.66(4\text{H}, \text{m}), 7.71(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.81(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.4\text{Hz}), 8.27(1\text{H}, \text{s}), 11.95(1\text{H}, \text{s})$.
IR(Nujol) : 1682 cm⁻¹.
mp : 102.8-104.5°C

30

Example 256 (Reference example)

Synthesis of 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole (318)

35 [0715] In the same manner as in Production Example 14, ethyl 4-[N-(2,4-dichlorobenzyl)acetylamino]-3-nitrobenzoate was formed from 1.525 g of ethyl 4-acetylamino-3-nitrobenzoate and 1.42 g of 2,4-dichlorobenzyl chloride. This compound was converted into 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole [(318), 1.476 g] in the same manner as in Example 24 without being purified.

[0716] Properties of Compound (318):

40

$^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.42(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.57(3\text{H}, \text{s}), 4.41(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.38(2\text{H}, \text{s}), 6.35(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.09(1\text{H}, \text{dd}, J=2.0 \text{ and } 8.4\text{Hz}), 7.16(1\text{H}, \text{d}, J=8.9\text{Hz}), 7.49(1\text{H}, \text{d}, J=2.0\text{Hz}), 7.96(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.46(1\text{H}, \text{s})$.

45

Example 257 (Reference example)

Synthesis of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (319)

50 [0717] In the same manner as in Example 53, 1.195 g of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (319) were formed from 1.465 g of 1-(2,4-dichlorobenzyl)-5-ethoxycarbonyl-2-methylbenzimidazole.

[0718] Properties of Compound (319):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.48(3\text{H}, \text{s}), 5.56(2\text{H}, \text{s}), 6.53(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.32(1\text{H}, \text{dd}, J=2.1 \text{ and } 8.4\text{Hz}), 7.44(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.73(1\text{H}, \text{d}, J=2.2\text{Hz}), 7.78(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.15(1\text{H}, \text{d}, J=1.3\text{Hz})$

55

Example 258

Synthesis of 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (320)

- 5 [0719] In the same manner as in Example 98, 0.690 g of 5-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (320) were formed from 0.565 g of 5-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.504 g of N,N'-carbonyldiimidazole, 0.427 g of 1-butanesulfonamide and 0.473 g of diazabicycloundecene.

[0720] Properties of Compound (320):

- 10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.87(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.41(2\text{H}, \text{m}), 1.68(2\text{H}, \text{m}), 2.49(3\text{H}, \text{s}), 3.52(2\text{H}, \text{m}), 5.58(2\text{H}, \text{s}), 6.53(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.33(1\text{H}, \text{dd}, J=2.1 \text{ and } 8.4\text{Hz}), 7.50(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.73(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.78(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.24(1\text{H}, \text{s}), 11.97(1\text{H}, \text{br s}).$
 IR(Nujol) : 1674 cm⁻¹.
 mp : 135.4-139.2°C

Example 259 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole (321)

- 20 [0721] In the same manner as in Production Example 14, ethyl 4-[N-(4-biphenylmethyl)propionylamino]-3-nitrobenzoate was formed from 1.50 g of 4-propionylamino-3-nitrobenzoate and 1.67 g of 4-bromomethylbiphenyl. This compound was converted into 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole [(321), 1.23 g] in the same manner as in Example 24 without being purified.

[0722] Properties of Compound (321):

- 25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.45(3\text{H}, \text{t}, J=7.6\text{Hz}), 2.90(2\text{H}, \text{q}, J=7.6\text{Hz}), 4.39(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.40(2\text{H}, \text{s}), 7.09(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.27(1\text{H}, \text{d}, J=8.8\text{Hz}), 7.34(1\text{H}, \text{m}), 7.42(2\text{H}, \text{t}), 7.55-7.51(4\text{H}, \text{m}), 7.97(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.52(1\text{H}, \text{d}, J=1.2\text{Hz})$

Example 260 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole (322)

- 30 [0723] In the same manner as in Example 53, 0.870 g of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole (322) were formed from 1.00 g of 1-(4-biphenylmethyl)-5-ethoxycarbonyl-2-ethylbenzimidazole.

[0724] Properties of Compound (322):

- 35 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.30(3\text{H}, \text{t}, J=7.4\text{Hz}), 2.90(2\text{H}, \text{q}, J=7.4\text{Hz}), 5.57(2\text{H}, \text{s}), 7.17(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.33(1\text{H}, \text{m}), 7.42(2\text{H}, \text{t}), 7.63-7.57(5\text{H}, \text{m}), 7.81(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.6\text{Hz}), 8.18(1\text{H}, \text{d}, J=1.3\text{Hz}), 12.67(1\text{H}, \text{br s})$

Example 261

Synthesis of 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (323)

- 40 [0725] In the same manner as in Example 98, 0.305 g of 1-(4-biphenylmethyl)-5-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole (323) were formed from 0.400 g of 1-(4-biphenylmethyl)-5-carboxy-2-ethylbenzimidazole, 0.364 g of N,N'-carbonyldiimidazole, 0.308 g of 1-butanesulfonamide and 0.342 g of diazabicycloundecene.

[0726] Properties of Compound (323):

- 45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.86(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.30(3\text{H}, \text{t}, J=7.5\text{Hz}), 1.41(2\text{H}, \text{m}), 1.68(2\text{H}, \text{m}), 2.91(2\text{H}, \text{q}, J=7.4\text{Hz}), 3.52(2\text{H}, \text{m}), 5.59(2\text{H}, \text{s}), 7.16(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.34(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.43(2\text{H}, \text{t}), 7.59-7.65(5\text{H}, \text{m}), 7.80(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.6\text{Hz}), 8.24(1\text{H}, \text{d}, J=1.6\text{Hz}), 11.97(1\text{H}, \text{br s}).$
 IR(Nujol) : 1682 cm⁻¹.
 mp : 142.9-144.4°C

Example 262

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxyethanesulfonylcarbamoyl)benzimidazole (324)

5 [0727] In the same manner as in Example 98, 0.487 g of 1-(4-biphenylmethyl)-2-ethyl-6-(2-methoxyethanesulfonylcarbamoyl)-benzimidazole (324) were formed from 0.513 g of benzimidazole, 0.464 g of N,N'-carbonyldiimidazole, 0.420 g of 2-methoxyethanesulfonamide and 0.438 g of diazabicycloundecene.

[0728] Properties of Compound (324):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.30(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.90(2\text{H}, \text{q}, J=7.4\text{Hz}), 3.13(3\text{H}, \text{s}), 3.70-3.77(4\text{H}, \text{m}), 5.60(2\text{H}, \text{s})$
 7.18(2H, d, J=8.2Hz), 7.35(1H, t, J=7.1Hz), 7.44(2H, t, J=7.5Hz), 7.60-7.67(4H, m), 7.70(1H, d, J=8.5Hz), 7.80
 (1H, dd, J=7.4 and 1.3Hz), 8.25(1H, s), 11.97(1H, s).
 IR(Nujol) : 1684cm⁻¹.
 mp : 94.6-97.2°C

Example 263 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole (325)

20 [0729] A mixture of 0.534 g of ethyl 4-propionylamino-3-aminobenzoate, 0.374 g of potassium carbonate, 0.800 g of 4-(4-fluorobenzylxy)benzyl bromide, 5 ml of ethyl acetate and 3 ml of water was stirred at 75°C for 16 hours. The organic layer was concentrated, and ethanol and 0.46 g of 36% hydrochloric acid were added to the residue. The mixture was stirred for 2 hours while being heat-refluxed. The reaction mixture was neutralized with potassium carbonate, and the solvent was then concentrated under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated under reduced pressure, and was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 1:1) to give 0.228 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole (325).

[0730] Properties of Compound (325):

30 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.42(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.86(2\text{H}, \text{q}, J=7.5\text{Hz}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 4.97$
 (2H, s), 5.32(2H, s), 6.88(2H, d, J=8.7Hz), 6.98(2H, d, J=8.7Hz), 7.05(2H, t, J=8.7Hz), 7.37(2H, m), 7.76(2H, d,
 J=8.4Hz), 7.98(1H, dd, J=1.5 and 8.5Hz), 8.02(1H, s)

Example 264 (Reference example)

Synthesis of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole (326)

[0731] In the same manner as in Example 53, 0.175 g of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole (326) were formed from 0.225 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole.

[0732] Properties of Compound (326):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.28(3\text{H}, \text{t}, J=7.4\text{Hz}), 2.89(2\text{H}, \text{q}, J=7.4\text{Hz}), 5.01(2\text{H}, \text{s}), 5.47(2\text{H}, \text{s}), 6.95(2\text{H}, \text{d}), 7.03$
 (2H, d), 7.18(2H, t), 7.45(2H, m), 7.62(1H, d, J=8.4Hz), 7.77(1H, d, J=8.4Hz), 8.05(1H, s)

Example 265

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole ammonium salt (327)

50 [0733] In the same manner as in Example 98, oily 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole was obtained from 0.171 g of 6-carboxy-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole, 0.137 g of N,N'-carbonyldiimidazole, 0.116 g of butanesulfonamide and 0.129 g of diazabicycloundecene. This compound was dissolved in ethyl acetate, and aqueous ammonia was added thereto. The solid material precipitated was separated through filtration, and was dried to give 0.140 g of 6-(1-butanesulfonylcarbamoyl)-2-ethyl-1-[4-(4-fluorobenzylxy)benzyl]benzimidazole ammonium salt (327).

[0734] Properties of Compound (327):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.83(3\text{H}, \text{t}), 1.25(3\text{H}, \text{t}), 1.35(2\text{H}, \text{m}), 1.61(2\text{H}, \text{m}), 2.84(2\text{H}, \text{q}), 3.27(2\text{H}, \text{m}), 5.01(2\text{H}, \text{s}),$

5.42(2H, s), 6.95(2H, d, J=7.8Hz), 7.02(2H, d, J=7.8Hz), 7.17(2H, t), 7.44(2H, m), 7.57(1H, d, J=8.1Hz), 7.82(1H, d, J=8.1Hz), 8.12(1H, s).
 IR(Nujol) : 1614cm⁻¹.
 mp : 105-115°C

5

Example 266 (Reference example)

Synthesis of 1-[4-(3,4-dichlorobenzyl)benzyl]-6-ethoxycarbonyl-2-ethylbenzimidazole (328)

10 [0735] In the same manner as in Example 263, 2.01 g of 1-[4-(3,4-dichlorobenzyl)benzyl]-6-ethoxycarbonyl-2-ethylbenzimidazole (328) were formed from 1.81 g of ethyl 4-propionylamino-3-aminobenzoate and 3.18 g of 4-(3,4-dichlorobenzyl)benzyl bromide.

[0736] Properties of Compound (328):

15 ¹H-NMR(CDCl₃, δ) : 1.40(3H, t, J=7.1Hz), 1.42(3H, t, J=7.5Hz), 2.86(2H, q, J=7.5Hz), 4.38(2H, q, J=7.1Hz), 4.97(2H, s), 5.33(2H, s), 6.87(2H, m), 6.98(2H, m), 7.22(1H, dd, J=2.0 and 8.3Hz), 7.44(1H, d, J=8.3Hz), 7.50(1H, d, J=2.0Hz), 7.76(1H, d, J=8.6Hz), 7.97(1H, dd, J=1.6 and 8.6Hz), 8.02(1H, d, J=1.3Hz)

20 Example 267 (Reference example)

Synthesis of 6-carboxy-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole (329)

25 [0737] In the same manner as in Example 53, 1.82 g of 6-carboxy-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole (329) were formed from 2.01 g of 6-ethoxycarbonyl-2-ethyl-1-[4-(4-fluorobenzyl)benzyl]benzimidazole.

[0738] Properties of Compound (329):

¹H-NMR(DMSO-d6, δ) : 1.28(3H, t), 2.88(2H, q), 5.05(2H, s), 5.47(2H, s), 6.96(2H, d), 7.04(2H, d), 7.39(1H, m), 7.68-7.59(3H, m), 7.78(1H, d, J=8.4Hz), 8.06(1H, s)

30 Example 268

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole ammonium salt (330)

35 [0739] Oily 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole was obtained from 0.500 g of 6-carboxy-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole, 0.356 g of N,N'-carbonyldiimidazole, 0.301 g of butanesulfonamide and 0.334 g of diazabicycloundecene in the same manner as in Example 98. This compound was dissolved in ethyl acetate, and aqueous ammonia was added thereto. The solid material precipitated was separated through filtration, and was dried to give 0.51 g of 6-(1-butanesulfonylcarbamoyl)-1-[4-(3,4-dichlorobenzyl)benzyl]-2-ethylbenzimidazole ammonium salt (330).

[0740] Properties of Compound (330):

40 ¹H-NMR(DMSO-d6, δ) : 0.82(3H, t, J=7.3Hz), 1.26(3H, t, J=7.4Hz), 1.31(2H, m), 1.54(2H, m), 2.84(2H, q, J=7.4Hz), 3.07(2H, m), 5.05(2H, s), 5.41(2H, s), 6.95(2H, d, J=8.7Hz), 7.00(2H, d, J=8.7Hz), 7.41(1H, d, J=8.2Hz), 7.46(1H, d, J=8.4Hz), 7.62(1H, d, J=8.2Hz), 7.68(1H, s), 7.81(1H, d, J=8.4Hz), 7.97(1H, s). IR(Nujol) : 1540cm⁻¹.
 mp : 99.5-101.5°C

45 Example 269 (Reference example)

50 Synthesis of 1-(4-biphenylmethyl)-6-(n-butylcarbamoyl)-2-ethylbenzimidazole (331)

[0741] In the same manner as in Example 15, 0.295 g of 1-(4-biphenylmethyl)-6-(n-butylcarbamoyl)-2-ethylbenzimidazole (331) were formed from 0.400 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.233 g of n-butylamine and 0.215 g of triethylamine.

[0742] Properties of Compound (331):

55 ¹H-NMR(DMSO-d6, δ) : 0.95(3H, t, J=7.3Hz), 1.37-1.48(2H, m), 1.45(3H, t, J=7.4Hz), 1.57-1.63(2H, m), 2.90(2H, q, J=7.5Hz), 3.46(2H, q, J=7.1Hz), 5.42(2H, s), 6.16(1H, br s), 7.10(2H, d, J=8.1Hz), 7.34(1H, t, J=7.5Hz), 7.42

(2H, t, J=7.5Hz), 7.48-7.57(5H, m), 7.87(1H, d, J=8.4Hz), 7.91(1H, s).
 IR(Nujol) : 1621cm⁻¹.
 mp : 170.5-173.0°C

5 Example 270 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(thiazol-2-yl-carbamoyl)benzimidazole (332)

10 **[0743]** In the same manner as in Example 15, 0.179 g of 1-(4-biphenylmethyl)-2-ethyl-6-(thiazol-2-ylcarbamoyl)benzimidazole (332) were obtained from 0.400 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.318 g of 2-aminothiazole and 0.215 g of triethylamine.

[0744] Properties of Compound (332):

15 ¹H-NMR(DMSO-d6, δ) : 1.48(3H, t, J=7.5Hz), 2.95(2H, q, J=7.5Hz), 5.41(2H, s), 6.94(1H, d, J=3.6Hz), 7.06(2H, d, J=8.1Hz), 7.26(1H, d, J=3.6Hz), 7.32(1H, t, J=7.4Hz), 7.39(2H, t, J=7.3Hz), 7.47-7.51(4H, m), 7.87(2H, s), 8.03(1H, s), 11.15(1H, s).
 IR(Nujol) : 1652cm⁻¹.
 mp : 225.5-227.7°C

20 Example 271 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(2-pyridylcarbamoyl)benzimidazole (333)

25 **[0745]** In the same manner as in Example 98, 0.116 g of 1-(4-biphenylmethyl)-2-ethyl-6-(2-pyridylcarbamoyl)benzimidazole (333) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 2-aminopyridine and 0.256 g of diazabicycloundecene.

[0746] Properties of Compound (333):

30 ¹H-NMR(CDCl₃, δ) : 1.47(3H, t, J=7.6Hz), 2.93(2H, q, J=7.4Hz), 5.45(2H, s), 7.06(1H, dd, J=7.4 and 4.9Hz), 7.10(2H, d, J=8.1Hz), 1.34(1H, t, J=7.4Hz), 7.42(2H, t, J=7.6Hz), 7.50-7.55(4H, m), 7.75(1H, t, J=7.9Hz), 7.79(1H, d, J=8.4Hz), 7.86(1H, d, J=8.4Hz), 7.98(1H, s), 8.30(1H, d, J=6.2Hz), 8.38(1H, d, J=8.4Hz), 8.62(1H,s).
 IR(Nujol) : 1661cm⁻¹.
 mp : 160.9-164.5°C

35 Example 272 (Reference example)

Synthesis of 6-(n-butylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (334)

40 **[0747]** In the same manner as in Example 15, 0.156 g of 6-(n-butylcarbamoyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (334) were formed from 0.300 g of 6-chlorocarbonyl-1-(2,4-dichlorobenzyl)-2-ethylbenzimidazole hydrochloride, 0.181 g of triethylamine and 0.196 g of n-butylamine.

[0748] Properties of Compound (334):

45 ¹H-NMR(CDCl₃, δ) : 0.96(3H, t, J=7.3Hz), 1.37-1.43(2H, m), 1.55-1.62(2H, m), 2.56(3H, s), 3.46(2H, q, J=7.0Hz), 5.40(2H, s), 6.15(1H, brs), 6.32(1H, d, J=8.5Hz), 7.07(1H, d, J=8.4Hz), 7.48(1H, d, J=2.0Hz), 7.55(1H, d, J=8.4Hz), 7.74(1H, d, J=8.4Hz), 7.79(1H,s).
 IR(Nujol) : 1636cm⁻¹.
 mp : 146.6-147.5°C

50 Production Example 53

Production of ethyl 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoate

55 **[0749]** A solution of 0.877 g of 3-fluoro-4-nitrobenzoic acid and 2.25 g of sec-(2,4-dichlorophenetyl)amine in 5ml of toluene was heat-refluxed for 15 hours. After the solvent was distilled off, the residue was purified through silica-gel column chromatography to obtain crude 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoic acid. To this compound were added 80 ml of ethanol and 3.0 g of 97% sulfuric acid, and the mixture was heat-refluxed for 4.5 hours. After ethanol was distilled off under reduced pressure, the residue was extracted with chloroform and with a saturated aque-

ous solution of sodium hydrogencarbonate. The organic layer was dried, and was then concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:1) to give 1.16 g of ethyl 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoate.

[0750] Properties of the compound:

⁵ $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.35(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.64(3\text{H}, \text{d}, J=6.6\text{Hz}), 4.30(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.16(1\text{H}, \text{m}), 7.18\text{--}7.31(4\text{H}, \text{m}), 7.43(1\text{H}, \text{d}, J=2.0\text{Hz}), 8.21(1\text{H}, \text{d}, J=8.8\text{Hz}), 8.34(1\text{H}, \text{d}, J=5\text{Hz})$

Production Example 54

¹⁰ Production of ethyl 4-amino-3-[sec-(2,4-dichlorophenetyl) amino]benzoate

[0751] A mixture of 1.14 g of ethyl 3-[sec-(2,4-dichlorophenetyl)amino]-4-nitrobenzoate, 1.60 g of reduced iron, 10 ml of ethanol and 5 ml of acetic acid was heat-refluxed for 3 hours. The solid material was separated through filtration, and the filtrate was concentrated. The residue was extracted with chloroform and with 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was purified through silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of 2:1) to give 0.920 g of ethyl 4-amino-3-[sec-(2,4-dichlorophenetyl)amino]benzoate.

[0752] Properties of the compound:

²⁰ $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.31(3\text{H}, \text{t}, J=7.1\text{Hz}), 1.52(3\text{H}, \text{d}, J=6.7\text{Hz}), 3.56(1\text{H}, \text{br s}), 3.79(2\text{H}, \text{br s}), 4.23(2\text{H}, \text{q}, J=7.1\text{Hz}), 4.96(1\text{H}, \text{q}, J=6.7\text{Hz}), 6.68(1\text{H}, \text{d}, J=8.0\text{Hz}), 7.03(1\text{H}, \text{d}, J=1.7\text{Hz}), 7.15(1\text{H}, \text{dd}, J=2.1 \text{ and } 8.4\text{Hz}), 7.35(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.39\text{--}7.43(2\text{H}, \text{m})$

Example 273 (Reference example)

Synthesis of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole (335)

³⁰ **[0753]** Acetyl chloride (0.243 g) was added dropwise to a solution of 0.900 g of ethyl 4-amino-3-[sec-(2,4-dichlorophenetyl)amino]benzoate in 2.0 ml of pyridine at room temperature. Further, the mixture was stirred at room temperature for 1 hour, and the reaction mixture was then extracted with the addition of ethyl acetate and excess 10% hydrochloric acid. The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure to obtain crude ethyl 4-acetylamino-3-[sec-(2,4-dichlorophenetyl)amino]benzoate. This crude product was immediately dissolved in 20 ml of ethanol, and 0.4 ml of 36% hydrochloric acid were added to the solution. The mixture was heat-refluxed for 2 hours. The reaction solution was neutralized with sodium hydrogencarbonate, and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and the residue was purified through silica-gel column chromatography (eluent: a mixture of ethyl acetate and methanol at a ratio of 20:1) to give 0.700 g of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole (335).

[0754] Properties of Compound (335):

⁴⁰ $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.38(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.01(3\text{H}, \text{d}, J=7.2\text{Hz}), 2.63(3\text{H}, \text{s}), 4.29\text{--}4.40(2\text{H}, \text{m}), 5.89(1\text{H}, \text{q}, J=7.2\text{Hz}), 7.37(1\text{H}, \text{dd}, J=2.2 \text{ and } 8.4\text{Hz}), 7.40(1\text{H}, \text{d}, J=2.0\text{Hz}), 7.52(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.67(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.86(1\text{H}, \text{s}), 7.91(1\text{H}, \text{dd}, J=1.4 \text{ and } 8.4\text{Hz})$

Example 274 (Reference example)

Synthesis of 6-carboxy-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (336)

⁵⁰ **[0755]** In the same manner as in Example 53, 0.447 g of 6-carboxy-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (336) were formed from 0.690 g of 1-[sec-(2,4-dichlorophenetyl)]-6-ethoxycarbonyl-2-methylbenzimidazole.

[0756] Properties of Compound (336):

⁵⁵ $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.88(3\text{H}, \text{d}, J=6.8\text{Hz}), 2.57(3\text{H}, \text{s}), 6.01(1\text{H}, \text{q}), 7.55(1\text{H}, \text{d}), 7.60\text{--}7.67(3\text{H}, \text{m}), 7.71(1\text{H}, \text{d}), 7.89(1\text{H}, \text{d}), 12.65(1\text{H}, \text{br s})$

Example 275

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (337)

5 [0757] In the same manner as in Example 98, 6-(1-butanesulfonylcarbamoyl)-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole (337) was formed from 0.433 g of 6-carboxy-1-[sec-(2,4-dichlorophenetyl)]-2-methylbenzimidazole, 0.412 g of N,N'-carbonyldiimidazole, 0.348 g of butanesulfonamide and 0.386 g of diazabicycloundecene.

[0758] Properties of Compound (337):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.84(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.34(2\text{H}, \text{m}), 1.57(2\text{H}, \text{m}), 1.89(3\text{H}, \text{d}, J=7.0\text{Hz}), 2.49(3\text{H}, \text{s}), 3.07(2\text{H}, \text{m}), 5.954(1\text{H}, \text{q}, J=7.0\text{Hz}), 7.41(1\text{H}, \text{d}, J=8.7\text{Hz}), 7.56(1\text{H}, \text{dd}, J=2.1 \text{ and } 8.5\text{Hz}), 7.61(1\text{H}, \text{d}, J=2.1\text{Hz}), 7.74-7.79(3\text{H}, \text{m})$

Example 276 (Reference example)

15 Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(phenylcarbamoyl)-benzimidazole (338)

20 [0759] In the same manner as in Example 15, 0.195 g of 1-(4-biphenylmethyl)-2-ethyl-6-(phenylcarbamoyl)benzimidazole (338) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-chlorocarbonyl-2-ethylbenzimidazole hydrochloride, 0.243 g of triethylamine and 0.224 g of aniline.

[0760] Properties of Compound (338):

25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.47(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.93(2\text{H}, \text{q}, J=7.5\text{Hz}), 5.44(2\text{H}, \text{s}), 7.11(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.14(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.32-7.38(3\text{H}, \text{m}), 7.42(2\text{H}, \text{t}, J=7.4\text{Hz}), 7.51-7.54(4\text{H}, \text{m}), 7.63(2\text{H}, \text{d}, J=7.8\text{Hz}), 7.69(1\text{H}, \text{dd}, J=8.4 \text{ and } 1.6\text{Hz}), 7.84(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.88(1\text{H}, \text{br s}), 7.97(1\text{H}, \text{d}, J=1.5\text{Hz})$.

IR(Nujol) : 1647cm^{-1} .

mp : $171.7-172.1^\circ\text{C}$

Example 277 (Reference example)

30 Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-thiadiazol-2-ylcarbamoyl)benzimidazole (339)

35 [0761] In the same manner as in Example 98, 0.234 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-thiadiazol-2-ylcarbamoyl)-benzimidazole (339) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.170 g of 2-amino-1,3,4-thiadiazole and 0.256 g of diazabicycloundecene.

[0762] Properties of Compound (339):

40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.45(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.90(2\text{H}, \text{q}, J=7.5\text{Hz}), 5.53(2\text{H}, \text{s}), 7.07(2\text{H}, \text{d}, J=8.3\text{Hz}), 7.33(1\text{H}, \text{t}, J=7.5\text{Hz}), 7.40(2\text{H}, \text{t}, J=7.3\text{Hz}), 7.52(4\text{H}, \text{d}, J=8.2\text{Hz}), 7.89(1\text{H}, \text{d}, J=8.5\text{Hz}), 8.08(1\text{H}, \text{dd}, J=8.5 \text{ and } 1.6\text{Hz}), 8.34(1\text{H}, \text{d}, J=1.2\text{Hz}), 7.60(1\text{H}, \text{s}), 12.26(1\text{H}, \text{s})$.

IR(Nujol) : 1654cm^{-1} .

mp : $230.1-233.4^\circ\text{C}$

Example 278 (Reference example)

45 Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(tetrazol-5-ylcarbamoyl)benzimidazole (340)

50 [0763] In the same manner as in Example 98, 0.135 g of 1-(4-biphenylmethyl)-2-ethyl-6-(tetrazol-5-ylcarbamoyl)-benzimidazole (340) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.143 g of 5-aminotetrazole and 0.256 g of diazabicycloundecene.

[0764] Properties of Compound (340)

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.32(3\text{H}, \text{t}, J=7.5\text{Hz}), 2.93(2\text{H}, \text{q}, J=7.5\text{Hz}), 5.61(2\text{H}, \text{s}), 7.23(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.34(1\text{H}, \text{t}, J=7.49\text{Hz}), 7.44(2\text{H}, \text{t}, J=7.6\text{Hz}), 7.60-7.67(4\text{H}, \text{m}), 7.76(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.98(1\text{H}, \text{d}, J=8.6\text{Hz}), 8.46(1\text{H}, \text{s}), 12.30(1\text{H}, \text{s}), 15.95(1\text{H}, \text{s})$.

IR(Nujol) : 1667cm^{-1} .

mp : $273.1-276.0^\circ\text{C}$

Example 279 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-3-ylcarbamoyl)benzimidazole (341)

5 [0765] In the same manner as in Example 98, 0.224 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-3-ylcarbamoyl)-benzimidazole (341) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.141 g of 3-amino-1,3,4-triazole and 0.256 g of diazabicycloundecene.

[0766] Properties of Compound (341):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 1.33(3H, t, $J=7.4\text{Hz}$), 2.93(2H, q, $J=7.4\text{Hz}$), 5.63(2H, s), 7.17(2H, d, $J=8.3\text{Hz}$), 7.35(1H, t, $J=7.4\text{Hz}$), 7.44(2H, t, $J=7.5\text{Hz}$), 7.60-7.65(4H, m), 7.78(1H, d, $J=7.4\text{Hz}$), 7.83(1H, dd, $J=8.4$ and 1.5Hz), 8.17(1H, s), 8.77(2H, s), 12.04(1H, s).

IR(Nujol) : 1675 cm^{-1} .

mp : 263.4-266.2 $^\circ\text{C}$

15

Example 280 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-2-ylcarbamoyl)benzimidazole (342)

20 [0767] In the same manner as in Example 98, 0.215 g of 1-(4-biphenylmethyl)-2-ethyl-6-(1,3,4-triazol-2-ylcarbamoyl)-benzimidazole (342) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.141 g of 2-amino-1,3,4-triazole and 0.256 g of diazabicycloundecene.

[0768] Properties of Compound (342):

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 1.31(3H, t, $J=7.4\text{Hz}$), 2.92(2H, q, $J=7.4\text{Hz}$), 5.60(2H, s), 7.23(2H, d, $J=7.8\text{Hz}$), 7.34(1H, t, $J=7.2\text{Hz}$), 7.44(2H, t, $J=7.6\text{Hz}$), 7.60-7.66(4H, m), 7.72(1H, d, $J=8.3\text{Hz}$), 7.78(1H, s), 7.95(1H, d, $J=8.3\text{Hz}$), 8.43(1H, s), 11.85(1H, s), 13.57(1H, s).

IR(Nujol) : 1659 cm^{-1} .

mp : 306.0 $^\circ\text{C}$ (decomp.)

30

Example 281 (Reference example)

Synthesis of 1-(4-biphenylinethyl)-2-ethyl-6-(3-pyridylcarbamoyl)benzimidazole (343)

35 [0769] In the same manner as in Example 98, 0.229 g of 1-(4-biphenylmethyl)-2-ethyl-6-(3-pyridylcarbamoyl)benzimidazole (343) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 3-aminopyridine and 0.256 g of diazabicycloundecene.

[0770] Properties of Compound (343):

40 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 1.47(3H, t, $J=7.6\text{Hz}$), 2.93(2H, q, $J=7.4\text{Hz}$), 5.45(2H, s), 7.10(2H, d, $J=8.1\text{Hz}$), 7.29-7.36(2H, m), 7.42(2H, t, $J=7.4\text{Hz}$), 7.53(4H, d, $J=8.0\text{Hz}$), 7.71(1H, d, $J=8.5\text{Hz}$), 7.86(1H, d, $J=8.4\text{Hz}$), 7.97(1H, s), 7.98(1H, s), 8.27(1H, d, $J=8.4\text{Hz}$), 8.38(1H, d, $J=4.7\text{Hz}$), 8.68(1H, d, $J=2.5\text{Hz}$).

IR(Nujol) : 1644 cm^{-1} .

mp : 124.4-125.6 $^\circ\text{C}$

45

Example 282 (Reference example)

Synthesis of 1-(2,4-dichlorobenzyl)-2-methyl-6-(2-pyridylcarbamoyl)benzimidazole (344)

50 [0771] In the same manner as in Example 98, 0.152 g of 1-(2,4-dichlorobenzyl)-2-methyl-6-(2-pyridylcarbamoyl)benzimidazole (344) were formed from 0.300 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 0.290 g of N,N'-carbonyldiimidazole, 0.168 g of 2-aminopyridine and 0.273 g of diazabicycloundecene.

[0772] Properties of Compound (344):

55 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 2.59(3H, s), 5.43(2H, s), 6.33(1H, d, $J=8.4\text{Hz}$), 7.06-7.10(2H, m), 7.50(1H, d, $J=2.1\text{Hz}$), 7.77(1H, dt, $J=7.8$ and 1.9Hz), 7.83(2H, s), 7.88(1H, s), 8.30(1H, d, $J=3.7\text{Hz}$), 8.39(1H, d, $J=8.3\text{Hz}$), 8.78(1H, s).

IR(Nujol) : 1666 cm^{-1} .

mp : 157.4-159.2 $^\circ\text{C}$

Example 283 (Reference example)

Synthesis of 1-(4-biphenylmethyl)-2-ethyl-6-(4-pyridylcarbamoyl)benzimidazole (345)

5 [0773] In the same manner as in Example 98, 0.153 g of 1-(4-biphenylmethyl)-2-ethyl-6-(4-pyridylcarbamoyl)benzimidazole (345) were formed from 0.300 g of 1-(4-biphenylmethyl)-6-carboxy-2-ethylbenzimidazole, 0.272 g of N,N'-carbonyldiimidazole, 0.158 g of 4-aminopyridine and 0.256 g of diazabicycloundecene.

[0774] Properties of Compound (345):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.48(3\text{H}, \text{t}, J=7.4\text{Hz}), 2.94(2\text{H}, \text{q}, J=7.4\text{Hz}), 5.45(2\text{H}, \text{s}), 7.10(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.35(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.42(2\text{H}, \text{t}, J=7.4\text{Hz}), 7.50-7.60(6\text{H}, \text{m}), 7.691(1\text{H}, \text{d}, J=7.8\text{Hz}), 7.86(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.95(1\text{H}, \text{s}), 7.99(1\text{H}, \text{br s}), 8.54(2\text{H}, \text{dd}, J=1.5 \text{ and } 4.7\text{Hz})$.
 IR(Nujol) : 1663 cm⁻¹.
 mp : 123.8-124.7°C

Production Example 55

Production of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide

20 [0775] In the same manner as in Production Example 28, 10.75 g of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide were formed from 10.0 g of 4-acetylamino-3-nitrobenzoic acid, 9.40 g of N,N'-carbonyldiimidazole, 7.92 g of 1-butanesulfonamide and 8.83 g of diazabicycloundecene.

[0776] Properties of the compound:

25 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.87(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.37-1.44(2\text{H}, \text{m}), 1.64-1.71(2\text{H}, \text{m}), 2.12(3\text{H}, \text{s}), 3.52(2\text{H}, \text{t}, J=7.7\text{Hz}), 7.83(1\text{H}, \text{d}, J=8.6\text{Hz}), 8.21(1\text{H}, \text{dd}, J=8.6 \text{ and } 2.1\text{Hz}), 8.54(1\text{H}, \text{d}, J=2.2\text{Hz}), 10.56(1\text{H}, \text{s}), 12.32(1\text{H}, \text{s})$

Production Example 56

30 Production of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide

[0777] In the same manner as in Production Example 29, 3.04 g of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide were formed from 10.75 g of N-(1-butanesulfonyl)-4-acetylamino-3-nitrobenzamide.

[0778] Properties of the compound:

35 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.86(3\text{H}, \text{t}, J=7.3\text{Hz}), 1.33-1.43(2\text{H}, \text{m}), 1.59-1.67(2\text{H}, \text{m}), 2.07(3\text{H}, \text{s}), 3.37-3.43(2\text{H}, \text{t}), 5.12(2\text{H}, \text{br s}), 7.13(1\text{H}, \text{dd}, J=8.2 \text{ and } 2.0\text{Hz}), 7.28(1\text{H}, \text{d}, J=1.9\text{Hz}), 7.40(1\text{H}, \text{d}, J=8.3\text{Hz}), 9.09(1\text{H}, \text{s})$

Production Example 57

40 Production of N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl)benzylamino]benzamide

[0779] In the same manner as in Production Example 32, crude N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl)benzylamino]benzamide was obtained from 0.400 g of N-(1-butanesulfonyl)-3-amino-4-acetylaminobenzamide and 45 0.477 g of 2-[(4-bromomethyl)phenyl]pyridine. This product was used in the subsequent reaction at once.

Example 284

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)-benzyl]-2-methylbenzimidazole (346)

50 [0780] In the same manner as in Example 183, 0.330 g of 6-(1-butanesulfonylcarbamoyl)-1-[4-(2-pyridyl)benzyl]-2-methylbenzimidazole (346) were obtained from the above-mentioned crude N-(1-butanesulfonyl)-4-acetylamino-3-[4-(2-pyridyl)benzylamino]benzamide.
 [0781] Properties of Compound (346):

55 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.82(3\text{H}, \text{t}), 1.37-1.46(2\text{H}, \text{m}), 1.54-1.61(2\text{H}, \text{m}), 2.54(3\text{H}, \text{s}), 3.10(2\text{H}, \text{t}, J=7.8\text{Hz}), 5.57(2\text{H}, \text{s}), 7.19(2\text{H}, \text{d}, J=7.5\text{Hz}), 7.33(1\text{H}, \text{t}, J=5.2\text{Hz}), 7.49(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.82-7.87(2\text{H}, \text{m}), 7.90(1\text{H}, \text{d}, J=8.0\text{Hz}), 8.01-8.04(3\text{H}, \text{m}), 8.63(1\text{H}, \text{d}, J=4.2\text{Hz})$.

IR(Nujol) : 1722cm⁻¹.
mp : 292.4-298.4°C

Example 285 (Reference examples)

- 5 Synthesis of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (347) and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (348)
- 10 [0782] Four grams of 1-(2,4-dichlorobenzyl)-2-methylbenzimidazole were added to 20 ml of chlorosulfonic acid in an ice bath, and the mixture was stirred at room temperature for 24 hours and then at 80°C for 1.5 hours. The reaction solution was poured into ice water, and the gum solid material precipitated was separated through filtration to obtain a mixture of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (347) and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (348). This mixture was used in the subsequent reaction at once.

15 Example 286 (Reference examples)

- Synthesis of 5-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (349) and 6-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (350)
- 20 [0783] The mixture of 5-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-chlorosulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole obtained in Example 285 was immediately treated with 100 ml of 25% aqueous ammonia at room temperature for 1 hour. The solid material was separated through filtration to give 2.68 g of a mixture of 5-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (349) and 6-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (350) at a ratio of 1:1.
- 25 Properties of the mixture of Compound (349) and Compound (350):

¹H-NMR(CD 3 OD, δ) : 2.52(3/2H, s), 2.54(3/2H, s), 5.54(2H, s), 6.55(1H, d, J=6.9Hz), 7.17(1H, d, J=8.0Hz), 7.52(1H, s), 7.65-7.78(2H, m), 7.82(1/2H, s), 8.11(1/2H, s)

30 Example 287 (Reference examples)

- Synthesis of 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (351) and 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (352)
- 35 [0784] One milliliter of chloroform, 0.56 ml of triethylamine and 0.326 g of n-valeryl chloride were added to 0.500 g of a mixture of 5-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-amino sulfonyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole at a ratio of 1:1, and the mixture was stirred at room temperature for 48 hours. Water was added thereto to stop the reaction, and the reaction solution was extracted with chloroform. The organic layer was dried, concentrated, and purified through silica-gel column chromatography (eluent: a mixture of chloroform and methanol at a ratio of 95:5) to obtain 0.360 g of a mixture of 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole and 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole. Further, this mixture was purified through medium-pressure silica-gel column chromatography (eluent: a mixture of hexane and ethyl acetate at a ratio of from 1:1 to 1:4) to give 0.95 g of 6-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (351) and 0.45 g of 5-(n-valerylaminosulfonyl)-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole (352).
- 45 [0785] Properties of Compound (351):

¹H-NMR(DMSO-d6, δ) : 0.74(3H, t, J=7.3Hz), 1.09(2H, m), 1.31(2H, m), 2.10(2H, t, J=7.3Hz), 2.53(3H, s), 5.63(2H, s), 6.60(1H, d, J=8.4Hz), 7.32(1H, d, J=8.3Hz), 7.67-7.77(3H, m), 7.93(1H, s).
IR(KBr) : 1726cm⁻¹.
mp : 207.5-210.0°C.
Mass(FD) : m/e 454(M+1)

[0786] Properties of Compound (352):

- 55 ¹H-NMR(DMSO-d6, δ) : 0.75(3H, t, J=7.3Hz), 1.11(2H, m), 1.34(2H, m), 2.13(2H, t, J=7.4Hz), 2.51(3H, s), 5.59(2H, s), 6.57(1H, d, J=8.5Hz), 7.32(1H, dd, J=2.2 and 8.4Hz), 7.57(1H, d, J=8.6Hz), 7.67(1H, dd, J=1.6 and 8.6Hz), 7.73(1H, d, J=2.1Hz), 8.08(1H, d, J=1.6Hz).
IR(KBr) : 1706cm⁻¹.

mp : 213.0-216.0°C

Example 288 (Reference example)

5 Synthesis of 2,4-dimethyl-6-methoxycarbonylbenzimidazole

[0787] Methyl 4-acetylamino-5-amino-3-methylbenzoate was obtained from methyl 4-amino-3-methylbenzoate by the method described in Journal of Medicinal Chemistry, 1993, 36, 4040 - 4051. Subsequently, this compound was heat-refluxed in acetic acid for 2 hours to give 2,4-dimethyl-6-methoxycarbonylbenzimidazole.

10 [0788] Properties of the compound:

$^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.55(3\text{H}, \text{s}), 2.62(3\text{H}, \text{s}), 3.91(3\text{H}, \text{s}), 7.74(1\text{H}, \text{s}), 8.07(1\text{H}, \text{s}), 10.65(1\text{H}, \text{br s})$

Example 289 (Reference example)

15 Synthesis of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole (353)

[0789] A mixture containing 0.900 g of 2,4-dimethyl-6-methoxycarbonylbenzimidazole, 1.20 g of 2,4-dichlorobenzyl chloride, 0.200 g of sodium iodide, 0.610 g of potassium carbonate and 4 ml of N,N-dimethylformamide was stirred at 20 80°C for 16 hours. After the organic solvent was distilled off under reduced pressure, the residue was extracted with ethyl acetate and with water. The organic layer was concentrated, and was crystallized with the addition of hexane. The crystals were separated through filtration, and were dried to give 1.08 g of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole (353).

[0790] Properties of Compound (353):

25 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 2.58(3\text{H}, \text{s}), 2.71(3\text{H}, \text{s}), 3.90(3\text{H}, \text{s}), 5.39(2\text{H}, \text{s}), 6.30(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.07(1\text{H}, \text{dd}, J=8.4 \text{ and } 2.0\text{Hz}), 7.49(1\text{H}, \text{d}, J=2.0\text{Hz}), 7.75(1\text{H}, \text{s}), 7.81(1\text{H}, \text{s})$

Example 290 (Reference example)

30 Synthesis of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (354)

[0791] In the same manner as in Example 53, 0.435 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (354) were formed from 0.510 g of 1-(2,4-dichlorobenzyl)-2,4-dimethyl-6-methoxycarbonylbenzimidazole.

35 [0792] Properties of Compound (354):

1H-NMR(DMSO-d6, δ) : 2.51(3H, s), 2.55(3H, s), 5.57(2H, s), 6.49(1H, d, $J=8.4\text{Hz}$), 7.31(1H, dd, $J=8.4 \text{ and } 2.2\text{Hz}$), 7.62(1H, s), 7.72(1H, d, $J=2.0\text{Hz}$), 7.78(1H, s), 12.64(1H, br s)

40 Example 291

Synthesis of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (355)

[0793] In the same manner as in Example 98, 0.468 g of 6-(1-butanesulfonylcarbamoyl)-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole (355) were formed from 0.417 g of 6-carboxy-1-(2,4-dichlorobenzyl)-2,4-dimethylbenzimidazole, 0.290 g of N,N'-carbonyldiimidazole, 0.246 g of 1-butanesulfonamide and 0.273 g of diazabicycloundecene.

[0794] Properties of Compound (355):

1H-NMR(DMSO-d6, δ) : 0.84(3H, t, $J=7.4\text{Hz}$), 1.38(2H, m), 1.64(2H, m), 2.49(3H, s), 2.56(3H, s), 3.48(2H, t), 5.55(2H, s), 6.40(1H, d, $J=8.5\text{Hz}$), 7.31(1H, dd, $J=2.1 \text{ and } 8.4\text{Hz}$), 7.64(1H, s), 7.75(1H, d, $J=2.1\text{Hz}$), 7.90(1H, s), 11.79(1H, br s).

IR(Nujol) : 1682cm⁻¹.

mp : 180.0-181.5°C

Production Example 58

Production of 4-phenoxybenzyl alcohol

- 5 [0795] Sodium borohydride (0.48 g) was added to a solution of 4.96 g of 4-phenoxybenzaldehyde in 20 ml of ethanol, and the mixture was stirred at room temperature for 1.5 hours. After the completion of the concentration, the residue was extracted with tert-butylmethyl ether and with water. The organic layer was concentrated to give 4.84 g of 4-phenoxybenzyl alcohol.

[0796] Properties of the compound:

- 10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 4.67(2\text{H}, \text{d}, J=5.7\text{Hz}), 6.99-7.01(4\text{H}, \text{m}), 7.10(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.32-7.35(4\text{H}, \text{m})$

Production Example 59

- 15 Production of 4-phenoxybenzyl chloride

[0797] Thionyl chloride (13.34 g) was added to 4.06 g of 4-phenoxybenzyl alcohol, and the mixture was stirred at 80°C for 3.5 hours. After the completion of the concentration, the reaction mixture was extracted with ethyl acetate and with water. The organic layer was concentrated to give 4.31 g of 4-phenoxybenzyl chloride.

- 20 [0798] Properties of the compound:

$^1\text{H-NMR}(\text{CDCl}_3, \delta) : 4.58(2\text{H}, \text{s}), 6.96-7.03(4\text{H}, \text{m}), 7.11-7.14(1\text{H}, \text{m}), 7.32-7.37(4\text{H}, \text{m})$

Example 292 (Reference example)

- 25 Synthesis of 6-ethoxycarbonyl-2-methyl-1-(4-phenoxybenzyl)-benzimidazole (356)

[0799] In the same manner as in Example 263, 0.49 g of ethyl 4-acetylamino-3-[(4-phenoxy)benzylamino]benzoate were obtained from 0.56 g of ethyl 4-acetylamino-3-aminobenzoate, 0.33 g of sodium carbonate, 0.12 g of sodium iodide and 0.66 g of 4-phenoxybenzyl chloride. Subsequently, this compound was converted into 6-ethoxycarbonyl-2-methyl-1-(4-phenoxybenzyl)-benzimidazole [(356), 0.44 g].

[0800] Properties of ethyl 4-acetylamino-3-[(4-phenoxy)benzylamino]benzoate:

- 35 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.37(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.04(3\text{H}, \text{s}), 4.18(1\text{H}, \text{br s}), 4.31-4.36(4\text{H}, \text{m}), 6.98-7.02(4\text{H}, \text{m}), 7.09-7.12(1\text{H}, \text{m}), 7.27-7.51(8\text{H}, \text{m})$

[0801] Properties of Compound (356):

- 40 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.61(3\text{H}, \text{s}), 4.39(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.35(2\text{H}, \text{s}), 6.92-6.95(2\text{H}, \text{m}), 6.97-7.00(2\text{H}, \text{m}), 7.02(2\text{H}, \text{d}, J=8.7\text{Hz}), 7.09-7.13(1\text{H}, \text{m}), 7.31-7.34(2\text{H}, \text{m}), 7.72(1\text{H}, \text{d}, J=8.6\text{Hz}), 7.98(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.04(1\text{H}, \text{d}, J=1.2\text{Hz})$

Example 293 (Reference example)

- 45 Synthesis of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole (357)

[0802] In the same manner as in Example 53, 0.37 g of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole (357) were formed from 0.44 g of 6-ethoxycarbonyl-2-methyl-1-(4-phenoxy)benzylbenzimidazole.

[0803] Properties of Compound (357):

- 50 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.57(3\text{H}, \text{s}), 5.54(2\text{H}, \text{s}), 6.95-6.97(4\text{H}, \text{m}), 7.09-7.13(3\text{H}, \text{m}), 7.33-7.37(2\text{H}, \text{m}), 7.60(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.78(1\text{H}, \text{d}, J=8.4\text{Hz}), 8.07(1\text{H}, \text{s}), 12.72(1\text{H}, \text{br s})$

Example 294

- 55 Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxybenzyl)benzimidazole (358)

[0804] In the same manner as in Example 98, 0.19 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(4-phenoxyben-

zyl)-benzimidazole (358) were obtained from 0.36 g of 6-carboxy-2-methyl-1-(4-phenoxybenzyl)benzimidazole, 0.24 g of N,N'-carbonyldiimidazole, 0.21 g of 1-butanesulfonamide and 0.23 g of diazabicycloundecene.

[0805] Properties of Compound (358):

⁵ ¹H-NMR(DMSO-d₆, δ) : 0.85(3H, t, J=7.4Hz), 1.40(2H, m), 1.68(2H, m), 2.54(3H, s), 3.52(2H, t, J=7.8Hz), 5.51(2H, s), 6.96-6.98(4H, m), 7.11(1H, t, J=7.4Hz), 7.17(2H, d, J=8.6Hz), 7.34-7.37(2H, m), 7.64(1H, d, J=8.5Hz), 7.79(1H, dd, J=1.5 and 8.5Hz), 8.24(1H, s), 11.92(1H, br s).
IR(Nujol) : 1632cm⁻¹.
mp : 183.4-184.4°C

10

Example 295 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl) benzimidazole (359)

¹⁵ [0806] In the same manner as in Example 263, 0.656 g of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl)benzimidazole (359) were formed from 0.600 g of ethyl 4-acetylamino-3-aminobenzoate, 0.450 g of potassium carbonate, 0.122 g of sodium iodide and 0.413 g of 2-chloromethylpyridine. This compound was used in the subsequent reaction at once.

20

Example 296 (Reference example)

Synthesis of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole (360)

²⁵ [0807] In the same manner as in Example 53, 0.532 g of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole (360) were formed from 0.656 g of 6-ethoxycarbonyl-2-methyl-1-(2-pyridylmethyl) benzimidazole.

[0808] Properties of Compound (360):

¹H-NMR(DMSO-d₆, δ) : 2.56(3H, s), 5.56(2H, s), 7.22(1H, d, J=7.9Hz), 7.28(1H, dd, J=5.0 and 7.1Hz), 7.45(1H, d, J=8.3Hz), 7.74-7.79(2H, m), 7.95(1H, s), 8.48(1H, d, J=8.5Hz).

30

Example 297

Synthesis of 1-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl)benzimidazole (361)

³⁵ [0809] In the same manner as in Example 98, 0.142 g of 1-(butanesulfonylcarbamoyl)-2-methyl-1-(2-pyridylmethyl)-benzimidazole (361) were formed from 0.500 g of 6-carboxy-2-methyl-1-(2-pyridylmethyl)benzimidazole, 0.394 g of N, N'-carbonyldiimidazole, 0.334 g of 1-butanesulfonamide and 0.370 g of diazabicycloundecene.

[0810] Properties of Compound (361):

40

¹H-NMR(DMSO-d₆, δ) : 0.83(3H, t, J=7.3Hz), 1.28-1.36(2H, m), 1.52-1.58(2H, m), 2.55(3H, s), 3.06(2H, t, J=7.9Hz), 5.56(2H, s), 7.17(1H, d, J=7.8Hz), 7.29(1H, dd, J=4.2 and 7.3Hz), 7.43(1H, d, J=8.4Hz), 7.77(1H, dt, J=1.8 and 7.7Hz), 7.81(1H, dd, J=1.4 and 8.4Hz), 7.96(1H, s), 8.50(1H, d, J=4.7Hz).
IR(Nujol) : 1674cm⁻¹.
mp : 139°C (decomp.)

45

Example 298 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-methyl-1-(4-nitrobenzyl) benzimidazole (362)

⁵⁰ [0811] In the same manner as in Example 263, 0.51 g of 6-ethoxycarbonyl-2-methyl-1-(4-nitrobenzyl)benzimidazole (362) were formed from 0.67 g of ethyl 4-acetylamino-3-aminobenzoate, 0.39 g of sodium carbonate, 0.14 g of sodium iodide and 0.78 g of 4-nitrodibenzyl bromide.

[0812] Properties of Compound (362):

55

¹H-NMR(CDCl₃, δ) : 1.39(3H, t, J=7.1Hz), 2.59(3H, s), 4.38(2H, q, J=7.1Hz), 5.49(2H, s), 7.20(2H, d, J=8.6Hz), 7.76(1H, d, J=8.5Hz), 7.94(1H, d, J=1.1Hz), 8.01(1H, dd, J=1.4 and 8.5Hz), 8.20(2H, d, J=8.6Hz).

Example 299 (Reference example)

Synthesis of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (363)

5 [0813] Six milliliters of ethanol and 0.8 ml of acetic acid were added to 0.50 g of 1-(4-nitrobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 0.47 g of reduced iron, and the mixture was refluxed for 4.5 hours. The reaction mixture was extracted with water and with ethyl acetate. The organic layer was washed with water, dried, and then concentrated under reduced pressure to give 0.46 g of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole (363).

[0814] Properties of Compound (363):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.59(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.25(2\text{H}, \text{s}), 6.61(2\text{H}, \text{d}, J=8.6\text{Hz}), 6.87(2\text{H}, \text{d}, J=8.6\text{Hz}), 7.71(1\text{H}, \text{d}, J=8.3\text{Hz}), 7.96(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.05(1\text{H}, \text{d}, J=1.3\text{Hz}).$

Example 300 (Reference example)

Synthesis of 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (364)

15 [0815] A solution of 0.25 g of benzoyl chloride in 4 ml of chloroform was added to a solution of 0.45 g of 1-(4-aminobenzyl)-6-ethoxycarbonyl-2-methylbenzimidazole and 0.15 g of pyridine in 8 ml of chloroform, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was extracted with water and then with chloroform. The organic layer was concentrated under reduced pressure to give 0.33 g of 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (364).

[0816] Properties of Compound (364):

20 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.1\text{Hz}), 2.59(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.37(2\text{H}, \text{s}), 7.06(2\text{H}, \text{d}, J=8.5\text{Hz}), 7.46-7.50(2\text{H}, \text{m}), 7.53-7.57(1\text{H}, \text{m}), 7.61(2\text{H}, \text{d}, J=8.5\text{Hz}), 7.72(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.84-7.86(2\text{H}, \text{m}), 7.89(1\text{H}, \text{br s}), 7.98(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.5\text{Hz}), 8.03(1\text{H}, \text{s}).$

Example 301 (Reference example)

Synthesis of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole (365)

25 [0817] In the same manner as in Example 53, 0.28 g of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole (365) were formed from 0.31 g of 1-[(4-benzoylamino)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole.

[0818] Properties of the compound (365):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.58(3\text{H}, \text{s}), 5.52(2\text{H}, \text{s}), 7.12(2\text{H}, \text{d}, J=8.5\text{Hz}), 7.48-7.52(2\text{H}, \text{m}), 7.54-7.58(1\text{H}, \text{m}), 7.61(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.73(2\text{H}, \text{d}, J=8.6\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 7.90-7.92(2\text{H}, \text{m}), 8.07(1\text{H}, \text{d}, J=1.2\text{Hz}), 10.26(1\text{H}, \text{s}), 12.73(1\text{H}, \text{br s}).$

Example 302

Synthesis of 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (366)

35 [0819] In the same manner as in Example 98, 0.14 g of 1-[(4-benzoylamino)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (366) were obtained from 0.26 g of 1-[(4-benzoylamino)benzyl]-6-carboxy-2-methylbenzimidazole, 0.17 g of N,N'-carbonyldiimidazole, 0.14 g of 1-butanesulfonamide and 0.16 g of diazabicycloundecene.

[0820] Properties of Compound (366):

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.85(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.40(2\text{H}, \text{m}), 1.68(2\text{H}, \text{m}), 2.56(3\text{H}, \text{s}), 3.52(2\text{H}, \text{t}, J=7.8\text{Hz}), 5.50(2\text{H}, \text{s}), 7.15(2\text{H}, \text{d}, J=8.6\text{Hz}), 7.50(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.55-7.59(1\text{H}, \text{m}), 7.64(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.74(2\text{H}, \text{d}, J=8.6\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.5\text{Hz}), 7.90-7.92(2\text{H}, \text{m}), 8.24(1\text{H}, \text{d}, J=1.3\text{Hz}), 10.27(1\text{H}, \text{s}), 11.92(1\text{H}, \text{br s}).$

IR(Nujol) : 1693cm⁻¹.

mp : 267.5-268.1°C.

45

Example 303 (Reference example)

Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)-benzyl]benzimidazole (367)

5 [0821] In the same manner as in Example 263, 0.320 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]-benzimidazole (367) were formed from 0.405 g of ethyl 4-acetylamino-3-aminobenzoate, 0.253 g of potassium carbonate, 0.082 g of sodium iodide and 0.500 g of 4-chloromethylstilbene.

[0822] Properties of Compound (367):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.6(3\text{H}, \text{s}), 4.38(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.38(2\text{H}, \text{s}), 7.01-7.09(4\text{H}, \text{m}), 7.26(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.35(2\text{H}, \text{t}, J=7.5\text{Hz}), 7.45(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.49(2\text{H}, \text{d}, J=7.5\text{Hz}), 7.73(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.99(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.30(1\text{H}, \text{d}, J=1.2\text{Hz}).$

Example 304 (Reference example)

15 Synthesis of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)-benzyl]benzimidazole (368)

20 [0823] Five-percent palladium on carbon was added to a solution of 0.320 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]benzimidazole in 10 ml of ethanol in a nitrogen atmosphere, and the mixture was stirred in a hydrogen atmosphere for 23 hours. The solid material was separated through filtration, and the filtrate was concentrated to give 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole (368). This compound was used in the subsequent reaction at once.

Example 305 (Reference example)

25 Synthesis of 6-carboxy-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole (369)

[0824] In the same manner as in Example 53, 0.242 g of 6-carboxy-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole (369) were formed from 0.283 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole.

30 [0825] Properties of Compound (369) :

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.56(3\text{H}, \text{s}), 2.82(4\text{H}, \text{s}), 5.51(2\text{H}, \text{s}), 7.02(2\text{H}, \text{d}, J=8.1\text{Hz}), 7.11-7.27(7\text{H}, \text{m}), 7.61(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.78(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.04(1\text{H}, \text{s}), 12.72(1\text{H}, \text{s}).$

Example 306

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethyl)benzyl]benzimidazole (370)

40 [0826] In the same manner as in Example 98, 0.249 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethyl)benzyl]benzimidazole (370) were formed from 0.225 g of 6-carboxy-2-methyl-1-[4-(2-phenylethyl)benzyl]benzimidazole, 1.214 g of N,N'-carbonyldiimidazole, 0.167 g of 1-butanesulfonamide and 0.185 g of diazabicycloundecene.

[0827] Properties of Compound (370):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.86(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.35-1.42(2\text{H}, \text{m}), 1.63-1.71(2\text{H}, \text{m}), 2.53(3\text{H}, \text{s}), 2.83(4\text{H}, \text{s}), 3.52(2\text{H}, \text{t}, J=7.7\text{Hz}), 5.49(2\text{H}, \text{s}), 7.04(2\text{H}, \text{d}, J=8.0\text{Hz}), 7.12-7.25(7\text{H}, \text{m}), 7.64(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.7 \text{ and } 8.5\text{Hz}), 8.22(1\text{H}, \text{d}, J=1.3\text{Hz}), 11.92(1\text{H}, \text{s}).$

IR(Nujol) : 1682 cm⁻¹.

mp : 95.4-99.0°C.

Production Example 60

Production of 4-benzoylbenzyl bromide

50 [0828] In the same manner as in Production Example 48, 5.28 g of 4-benzoylbenzyl bromide were formed from 3.92 g of 4-methylbenzophenone, 4.28 g of N-bromosuccinimide and 0.40 g of 2,2'-azobisisobutyronitrile.

[0829] Properties of the compound:

$^1\text{H-NMR}(\text{CDCl}_3, \delta) : 4.54(2\text{H}, \text{s}), 7.47-7.52(4\text{H}, \text{m}), 7.58-7.62(1\text{H}, \text{m}), 7.77-7.82(4\text{H}, \text{m}).$

Example 307 (Reference example)

Synthesis of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (371)

5 [0830] In the same manner as in Example 263, 0.70 g of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole (371) were formed from 0.56 g of ethyl 4-acetylamino-3-aminobenzoate, 0.33 g of sodium carbonate, 0.11 g of sodium iodide and 0.83 g of 4-benzoylbenzyl bromide.

[0831] Properties of Compound (371):

10 $^1\text{H-NMR}(\text{CDCl}_3, \delta) : 1.40(3\text{H}, \text{t}, J=7.2\text{Hz}), 2.61(3\text{H}, \text{s}), 4.39(2\text{H}, \text{q}, J=7.2\text{Hz}), 5.47(2\text{H}, \text{s}), 7.14(2\text{H}, \text{d}, J=8.2\text{Hz}),$
 $7.45\text{--}7.48(2\text{H}, \text{m}), 7.56\text{--}7.60(1\text{H}, \text{m}), 7.74\text{--}7.77(5\text{H}, \text{m}), 7.99\text{--}8.02(2\text{H}, \text{m}).$

Example 308 (Reference example)

15 Synthesis of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole (372)

[0832] In the same manner as in Example 53, 0.55 g of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole (372) were formed from 0.68 g of 1-[(4-benzoyl)benzyl]-6-ethoxycarbonyl-2-methylbenzimidazole.

[0833] Properties of Compound (372):

20 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.57(3\text{H}, \text{s}), 5.71(2\text{H}, \text{s}), 7.25(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.52(2\text{H}, \text{t}, J=7.7\text{Hz}), 7.62\text{--}7.66(2\text{H}, \text{m}),$
 $7.68\text{--}7.72(4\text{H}, \text{m}), 7.80(1\text{H}, \text{dd}, J=1.3 \text{ and } 8.4\text{Hz}), 8.08(1\text{H}, \text{d}, J=1.1\text{Hz}), 12.72(1\text{H}, \text{br s}).$

Example 309

25 Synthesis of 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (373)

[0834] In the same manner as in Example 98, 0.13 g of 1-[(4-benzoyl)benzyl]-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (373) were formed from 0.52 g of 1-[(4-benzoyl)benzyl]-6-carboxy-2-methylbenzimidazole, 0.34 g of N,N'-carbonyldiimidazole, 0.29 g of 1-butanesulfonamide and 0.32 g of diazabicycloundecene.

[0835] Properties of Compound (373):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.84(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.38(2\text{H}, \text{m}), 1.66(2\text{H}, \text{m}), 2.54(3\text{H}, \text{s}), 3.48(2\text{H}, \text{t}, J=7.7\text{Hz}), 5.67$
 $(2\text{H}, \text{s}), 7.27(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.51\text{--}7.55(2\text{H}, \text{m}), 7.63\text{--}7.73(6\text{H}, \text{m}), 7.81(1\text{H}, \text{dd}, J=1.6 \text{ and } 8.5\text{Hz}), 8.21(1\text{H}, \text{d},$
 $J=1.4\text{Hz}).$

IR(Nujol) : 1660cm⁻¹.

mp : 111.0-112.4°C.

Mass(FAB) : m/e 490(M+1).

Example 310 (Reference example)

Synthesis of 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl]-benzimidazole (374)

[0836] In the same manner as in Example 53, 0.237 g of 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole (374) were formed from 0.500 g of 6-ethoxycarbonyl-2-methyl-1-[4-(2-phenylethenyl)benzyl]benzimidazole.

[0837] Properties of Compound (374):

40 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 2.59(3\text{H}, \text{s}), 5.58(2\text{H}, \text{s}), 7.12(2\text{H}, \text{d}, J=8.2\text{Hz}), 7.21(2\text{H}, \text{s}), 7.26(1\text{H}, \text{t}, J=7.4\text{Hz}), 7.36(2\text{H},$
 $\text{t}, J=7.6\text{Hz}), 7.57(4\text{H}, \text{d}, J=8.0\text{Hz}), 7.62(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.79(1\text{H}, \text{dd}, J=1.5 \text{ and } 8.4\text{Hz}), 8.07(1\text{H}, \text{d}, J=1.2\text{Hz}),$
 $12.73(1\text{H}, \text{s}).$

Example 311

Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole (375)

55 [0838] In the same manner as in Example 98, 0.239 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole (375) were formed from 0.237 g of 6-carboxy-2-methyl-[4-(2-phenylethenyl)benzyl]benzimidazole, 0.209 g of N,N'-carbonyldiimidazole, 0.176 g of 1-butanesulfonamide and 0.195 g of diazabicycloundecene.

[0839] Properties of Compound (375):

5 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.86(3H, t, $J=7.4\text{Hz}$), 1.35-1.43(2H, m), 1.63-1.70(2H, m), 2.56(3H, s), 3.52(2H, t, $J=7.6\text{Hz}$), 5.55(2H, s), 7.15(2H, d, $J=8.2\text{Hz}$), 7.22(2H, s), 7.26(1H, t, $J=7.4\text{Hz}$), 7.36(2H, t, $J=7.6\text{Hz}$), 7.57(1H, d, $J=7.3\text{Hz}$), 7.58(1H, d, $J=8.2\text{Hz}$), 7.66(1H, d, $J=8.5\text{Hz}$), 7.80(1H, d, $J=8.4\text{Hz}$), 8.24(1H, s), 11.93(1H, brs).
 IR(Nujol) : 1680cm $^{-1}$.
 mp : 140.3-143.4°C.

Example 312 (Reference example)

10 Synthesis of 1-(dibenzofuran-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (376)

15 **[0840]** In the same manner as in Example 263, 0.47 g of 1-(dibenzofuran-2-ylmethyl)-6-ethoxycarbonyl-2-methylbenzimidazole (376) were formed from 0.480 g of ethyl 4-acetylamino-3-aminobenzoate, 0.274 g of sodium carbonate, 0.097 g of sodium iodide and 0.56 g of 2-bromomethyldibenzofuran.

[0841] Properties of Compound (376):

20 $^1\text{H-NMR}(\text{CDCl}_3, \delta)$: 1.38(3H, t, $J=7.1\text{Hz}$), 2.62(3H, s), 4.36(2H, q, $J=7.1\text{Hz}$), 5.54(2H, s), 7.19(1H, dd, $J=1.6$ and 8.5Hz), 7.32(1H, t, $J=7.6\text{Hz}$), 7.43-7.59(4H, m), 7.76(1H, d, $J=8.4\text{Hz}$), 7.85(1H, d, $J=7.1\text{Hz}$), 8.00(1H, dd, $J=1.3$ and 8.4Hz), 8.07(1H, d, $J=1.2\text{Hz}$).

Example 313 (Reference example)

25 Synthesis of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole (377)

[0842] In the same manner as in Example 53, 0.336 g of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole (377) were formed from 0.46 g of 6-ethoxycarbonyl-2-methylbenzimidazole.

[0843] Properties of Compound (377):

30 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 2.63(3H, s), 5.71(2H, s), 7.27(1H, d, $J=8.5\text{Hz}$), 7.36(1H, t, $J=7.5\text{Hz}$), 7.50(1H, t), 7.61-7.68(3H, m), 7.78(1H, d, $J=8.3\text{Hz}$), 7.97(1H, s), 7.07-8.11(2H, m).

Example 314

35 Synthesis of 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (378)

40 **[0844]** In the same manner as in Example 98, 0.249 g of 1-(dibenzofuran-2-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole (378) were formed from 0.255 g of 6-carboxy-1-(dibenzofuran-2-ylmethyl)-2-methylbenzimidazole, 0.197 g of H,N'-carbonyldiimidazole, 0.167 g of 1-butanesulfonamide and 0.185 g of diazabicycloundecene.

[0845] Properties of Compound (378):

45 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$: 0.81(3H, t, $J=7.4\text{Hz}$), 1.36(2H, m), 1.65(2H, m), 2.60(3H, s), 3.50(2H, t, $J=7.7\text{Hz}$), 5.69(2H, s), 7.29(1H, dd, $J=1.96$ and 8.7Hz), 7.34-7.38(1H, m), 7.48-7.52(1H, m), 7.63-7.68(3H, m), 7.81(1H, dd, $J=1.7$ and 8.5Hz), 8.00(1H, d, $J=1.4\text{Hz}$), 8.94(1H, d, $J=7.1\text{Hz}$), 8.28(1H, d, $J=1.4\text{Hz}$), 12.70(1H, br s).
 IR(Nujol) : 1682cm $^{-1}$.

mp : 224.1-229.8°C.

Production Example 61

50 Production of N-1-butanesulfonyl-3-acetylamino-4-nitrobenzamide

55 **[0846]** In the same manner as in Production Example 28, 6.30 g of N-1-butanesulfonyl-3-acetylamino-4-nitrobenzamide were obtained from 5.15 g of 3-acetylamino-4-nitrobenzoic acid, 5.59 g of N,N'-carbonyldiimidazole, 4.73 g of 1-butanesulfonamide and 5.25 g of diazabicycloundecene.

[0847] Properties of the compound:

1H-NMR(DMSO-d₆, δ) : 0.87(3H, t, J=7.4Hz), 1.40(2H, m), 1.68(2H, m), 2.07(3H, s), 3.51(2H, t), 7.83(1H, dd, J=1.8 and 8.5Hz), 8.03(1H, d, J=8.5Hz), 8.07(1H, d, J=1.8Hz), 10.43(1H, s), 12.64(1H, br s).

Production Example 62

Production of N-1-butanesulfonyl-3-amino-4-nitrobenzamide

- 5 [0848] A mixture containing 6.30 g of N-1-butanesulfonyl-3-acetylamino-4-nitrobenzamide, a 10% sodium hydroxide aqueous solution, 300 ml of ethanol and 200 ml of water was stirred at room temperature for 4 hours and then at 50°C for 3 hours. The solvent was distilled off to approximately a half volume, and the residue was adjusted to a pH of 2 with 10% hydrochloric acid. The crystals precipitated were collected, and were dried under reduced pressure to give 5.22 g of N-1-butanesulfonyl-3-amino-4-nitrobenzamide.
- 10 [0849] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 0.87(3H, t, J=7.4Hz), 1.40(2H, m), 1.66(2H, m), 3.49(2H, m), 6.99(1H, dd, J=1.8 and 9.0Hz), 7.49(1H, d, J=1.8Hz), 7.55(2H, br s), 8.04(1H, d, J=9.0Hz), 12.28(1H, br s).

Production Example 63

Production of N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide

- 20 [0850] A solution containing 1.10 g of N-1-butanesulfonyl-3-amino-4-nitrobenzamide, 0.273 g of sodium iodide, 1.54 g of potassium carbonate, 2.17 g of 2,4-dichlorobenzyl chloride and 10 ml of methanol was stirred at 60°C for 24 hours. Further, 2.00 g of 2,4-dichlorobenzyl chloride were added thereto, and the mixture was heated at 60°C for 36 hours. To the reaction solution were added ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate, and N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide was extracted in the aqueous layer. The organic layer was concentrated to give 0.885 g of N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide.
- 25 [0851] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 0.81(3H, t, J=7.3Hz), 1.29(2H, m), 1.49(2H, m), 2.97(2H, m), 4.66(2H, d, J=6.0Hz), 7.22 (1H, d, J=8.9Hz), 7.27(1H, s), 7.31(1H, d, J=8.4Hz), 7.37(1H, d, J=8.3Hz), 7.65(1H, s), 8.04(1H, d, J=8.9Hz), 8.57 (1H, t).

Production Example 64

Production of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide

- 35 [0852] N-1-butanesulfonyl-3-(2,4-dichlorobenzylamino)-4-nitrobenzamide (0.505 g) was added to a mixture of 1.32 g of sodium hydrosulfite, 1 ml of ethanol, 1 ml of tetrahydrofuran and 1 ml of water at room temperature. The mixture was heat-refluxed for 40 minutes. The solvent was distilled off under reduced pressure, and water was added to the residue. The solid material precipitated was collected, and was dried. Further, the resulting material was washed with a mixed solution of 10 ml of methanol and 3 ml of water, and was dried to give 0.220 g of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide.
- 40 [0853] Properties of the compound:

¹H-NMR(DMSO-d₆, δ) : 0.93(3H, t, J=7.4Hz), 1.45(2H, m), 1.83(2H, m), 3.57(2H, m), 5.45(2H, s), 6.36(1H, d, J=8.2Hz), 7.11(1H, d, J=8.3Hz), 7.51(1H, s), 7.75(1H, d), 7.79(1H, d), 7.88(1H, s).

Example 315

Synthesis of 6-(1-butanesulfonylcaramoyl)-1-(2,4-dichlorobenzyl)-2-hydroxybenzimidazole (379)

- 50 [0854] A mixture of 0.220 mg of N-1-butanesulfonyl-4-amino-3-(2,4-dichlorobenzylamino)benzamide, 0.3 ml of tetramethoxymethane and 2.0 ml of acetic acid was stirred at 60°C for 4 hours. Acetic acid was distilled off under reduced pressure, and the residue was extracted with chloroform and with water. The chloroform layer was concentrated, and 4.0 ml of methanol and 36% hydrochloric acid (4 drops) were added to the residue. The mixture was stirred at 60°C for 2 hours. The reaction solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. 55 The crystals precipitated were washed with water, and were dried to give 0.207 g of 6-(1-butanesulfonylcaramoyl)-1-(2,4-dichlorobenzyl)-2-hydroxybenzimidazole (379).
- [0855] Properties of Compound (379):

5 ¹H-NMR(DMSO-d6, δ) : 0.83(3H, t, J=7.3Hz), 1.36(2H, m), 1.61(2H, m), 3.40(2H, m), 5.08(2H, s), 6.94(1H, d, J=8.3Hz), 7.11(1H, d, J=8.2Hz), 7.36(1H, dd, J=2.0 and 8.4Hz), 7.58(1H, s), 7.68-7.73(2H, m), 11.47(1H, br s), 11.77(1H, br s).
 IR(Nujol) : 1689cm⁻¹.
 mp : 254-256°C.
 Mass(FD) : m/e 455(M).

Example 316 (Reference example)

10 Synthesis of 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl)-benzimidazole (380)

[0856] In accordance with Example 263, 0.87 g of 6ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl)benzimidazole (380) were formed from 2.22 g of ethyl 4-acetylamino-3-aminobenzoate, 1.27 g of sodium carbonate, 0.45 g of sodium iodide and 2.28 g of 2-bromomethylquinoline.

15 [0857] Properties of the compound (380):

20 ¹H-NMR(DMSO-d6, δ) : 1.27(3H, t, J=7.1Hz), 2.62(3H, s), 4.26(2H, q, J=7.1Hz), 5.85(2H, s), 7.35(1H, d, J=8.5Hz), 7.58(1H, m), 7.63(1H, d, J=8.4Hz), 7.73(1H, m), 7.78(1H, dd, J=1.3 and 8.4Hz), 7.86(1H, d, J=8.4Hz), 7.95(1H, d, J=8.0Hz), 8.14(1H, s), 8.36(1H, d, J=8.5Hz).

25 Example 317 (Reference example)

Synthesis of 6-carboxy-2-methyl-(2-quinolylmethyl)benzimidazole (381)

25 [0858] In the same manner as in Example 53, 0.46 g of 6-carboxy-2-methyl-(2-quinolylmethyl)benzimidazole (381) were formed from 0.85 g of 6-ethoxycarbonyl-2-methyl-1-(2-quinolylmethyl) benzimidazole.

[0859] Properties of Compound (381):

30 ¹H-NMR(DMSO-d6, δ) : 2.62(3H, s), 5.83(2H, s), 7.35(1H, d, J=8.5Hz), 7.57(1H, m), 7.60(1H, d, J=8.5Hz), 7.72 (1H, t, J=7.6Hz), 7.77(1H, d, J=8.4Hz), 7.86(1H, d, J=8.4Hz), 7.94(1H, d, J=8.1Hz), 8.11(1H, s), 8.35(1H, d, J=8.5Hz).

Example 318

35 Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmethyl)benzimidazole (382)

[0860] In the same manner as in Example 98, 0.088 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-(2-quinolylmeth-40 yl)-benzimidazole (382) were formed from 0.222 g of 6-carboxy-2-methyl-1-(2-quinolylmethyl)benzimidazole, 0.195 g of N,N'-carbonyldiimidazole, 0.165 g of 1-butanesulfonamide and 0.183 g of diazabicycloundecene.

[0861] Properties of Compound (382):

45 ¹H-NMR(DMSO-d6, δ) : 0.82(3H, t, J=7.3Hz), 1.36(2H, m), 1.64(2H, m), 2.61(3H, s), 3.48(2H, t, J=7.4Hz), 5.82 (2H,s), 7.32(1H, d, J=8.5Hz), 7.58(1H, m), 7.65(1H, d, J=8.5Hz), 7.73(1H, t, J=7.6Hz), 7.78(1H, m), 7.87(1H, d, J=8.5Hz), 7.95(1H, d, J=8.1Hz), 8.23(1H, s), 8.37(1H, d, J=8.5Hz), 11.86(1H, brs).

45 IR(Nujol) : 1684cm⁻¹.
 mp : 185.5-187.5°C.

Production Example 65

50 Production of ethyl 4-amino-3-(2,4-dichlorobenzylamino)benzoate

[0862] Crude ethyl 4-amino-3-(2,4-dichlorobenzylamino)benzoate was formed from 1.40 g of 3-(2,4-dichloroben-zylamino)-4-nitrobenzoate and 4.50 g of sodium hydrosulfite in the same manner as in Production Example 64. This compound was used in the subsequent reaction at once.

Example 319 (Reference example)

Synthesis of 1-(2,4-dichlorobenzylamino)-2-hydroxy-6-ethoxycarbonylbenzimidazole (383)

5 [0863] In the same manner as in Example 315, 0.400 g of 1-(2,4-dichlorobenzylamino)-2-hydroxy-6-ethoxycarbonylbenzimidazole (383) were formed from ethyl 4-amino-3-(2,4-dichlorobenzylamino)benzoate obtained in the above-mentioned Production Example 63 and 2.60 g of tetramethoxymethane.

[0864] Properties of Compound (383):

10 $^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.27(3\text{H}, \text{t}, J=7.1\text{Hz}), 4.24(2\text{H}, \text{q}, J=7.1\text{Hz}), 5.12(2\text{H}, \text{s}), 7.04(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.12(1\text{H}, \text{d}, J=8.2\text{Hz}), 7.37(1\text{H}, \text{dd}, J=2.1 \text{ and } 8.4\text{Hz}), 7.51(1\text{H}, \text{s}), 7.67-7.72(2\text{H}, \text{m}), 11.37(1\text{H}, \text{br s})$

Example 320 (Reference example)

15 Synthesis of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (384)

[0865] In the same manner as in Example 263, 0.30 g of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]-benzimidazole (384) were formed from 0.87 g of ethyl 4-acetylamino-3-aminobenzoate, 0.53 g of sodium carbonate, 0.18 g of sodium iodide and 0.87 g of 4-bromo-3-bromomethylisoquinoline.

20 [0866] Properties of Compound (384):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 1.26(3\text{H}, \text{t}, J=7.0\text{Hz}), 2.59(3\text{H}, \text{s}), 4.24(2\text{H}, \text{q}, J=7.0\text{Hz}), 5.93(2\text{H}, \text{s}), 7.61(1\text{H}, \text{d}, J=8.4\text{Hz}), 7.75-7.80(2\text{H}, \text{m}), 7.99(1\text{H}, \text{m}), 8.03(1\text{H}, \text{s}), 8.13(1\text{H}, \text{d}, J=8.1\text{Hz}), 8.23(1\text{H}, \text{d}, J=8.5\text{Hz}), 9.12(1\text{H}, \text{s})$.

Example 321 (Reference example)

Synthesis of 6-carboxy-2-methyl-[3-(4-bromoisoquinolyl)methyl]-benzimidazole (385)

30 [0867] In the same manner as in Example 53, 0.118 g of 6-carboxy-2-methyl-[3-(4-bromoisoquinolyl)methyl]benzimidazole (385) were formed from 0.290 g of 6-ethoxycarbonyl-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole. This compound was used in the subsequent reaction at once.

Example 322

35 Synthesis of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (386)

[0868] In the same manner as in Example 98, 0.075 g of 6-(1-butanesulfonylcarbamoyl)-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole (386) were formed from 0.111 g of 6-carboxy-2-methyl-1-[3-(4-bromoisoquinolyl)methyl]benzimidazole, 0.097 g of N,N'-carbonyldiimidazole, 0.082 g of 1-butanesulfonamide and 0.091 g of diazabicycloundecene.

40 [0869] Properties of Compound (386):

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta) : 0.81(3\text{H}, \text{t}, J=7.4\text{Hz}), 1.35(2\text{H}, \text{m}), 1.62(2\text{H}, \text{m}), 2.54(3\text{H}, \text{s}), 3.46(2\text{H}, \text{t}, J=7.5\text{Hz}), 5.91(2\text{H}, \text{s}), 7.63(1\text{H}, \text{d}, J=8.5\text{Hz}), 7.76(1\text{H}, \text{dd}, J=8.5 \text{ and } 1.4\text{Hz}), 7.79(1\text{H}, \text{t}, J=7.6\text{Hz}), 8.00(1\text{H}, \text{t}, J=7.9\text{Hz}), 8.08(1\text{H}, \text{t}, J=1.1\text{Hz}), 8.13(1\text{H}, \text{d}, J=8.2\text{Hz}), 8.24(1\text{H}, \text{d}, J=8.5\text{Hz}), 9.11(1\text{H}, \text{s}), 11.81(1\text{H}, \text{brs}).$

IR(Nujol) : 1678cm⁻¹.

mp : 258-259°C.

Mass(FAB) : m/e 515, 517(M+1).

50 [0870] From among the compounds of the present invention, the typical compounds were selected, and were tested for pharmacological properties.

Test Example 1

55 [0871]

Stimulatory activity of triglyceride (TG) accumulation in 3T3-L1 cells (pre-adipocytes)

Test compound

[0872]

5 6-benzylsulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole

Devices used

[0873]

1. Centrifuge: TOMY LC-122
 2. Incubator: ESPEC BNA-121D
 3. Mixer: Automatic Labo-Mixer
 4. Water bath: TAITEC PERSONAL-11
 5. spectrophotometer: Shimadzu UV Visible Spectrophotometer UV-160A
 6. 24-well plate: IWAKI GLASS CORNING

Reagents used

20 [0874]

1. Medium: Dulbecco minimum essential medium (MEM) + 5% fetal calf serum (FCS)
 2. PBS (-): solution having the following composition NaCl 0.8 g/liter KCl 0.2 Na_2HPO_4 1.15
 KH_2PO_4 0.2
 3. Solution of EDTA and trypsin:
 0.02% EDTA + 0.25% trypsin/PBS(-)
 4. Dexamethasone: made by Sigma
 5. IBMX (3-isobutyl-1-methylxanthine): made by Sigma
 6. Insulin: made by Sigma
 7. DMSO (dimethylsulfoxide): made by Wako Pure Chemical Industries, Ltd.
 8. TG measuring kit:
Triglyceride-Test Wako (acetyl-acetone method): made by Wako Pure Chemical Industries, Ltd
 9. 0.1-N NaOH solution:
prepared by diluting a 1N NaOH solution to 10 times with distilled water.
 10. Bio-Rad Protein Assay Reagent: made by Bio-Rad.
 11. Bovine albumin: made by Sigma

Test method

40 Preparation of 3T3-L1 cells

[0875] 3T3-L1 cells just before a confluent state were prepared in an F75 flask. The medium was removed, and the residue was washed twice with 5 ml of PBS (-). The cells were detached using a solution of EDTA and trypsin. Ten milliliters of the medium were added thereto to form a suspension. This suspension was collected in a 50-milliliter centrifuge tube, and was subjected to centrifugation at 1,000 rpm for 5 minutes. Thus, the cells were precipitated, and the supernatant was removed. The cells were re-suspended in 20 ml of the medium, and the number of cells was counted. The suspension was adjusted such that the concentration of the cells reached 6×10^4 cells/ml, and was inoculated into a 24-well plate in an amount of 1 ml/well. In this state, the incubation was conducted in an incubator at 37°C in 5% CO₂ for 2 days.

Preparation and addition of dexamethasone and IBMX

[0876] A solution of 1-mM dexamethasone and 500-mM IBMX was prepared in DMSO. Further, this solution was diluted to 1,000 times with the medium to form a solution of 1 μ M dexamethasone and 0.5mM IBMX. At the same time, DMSO was diluted with the medium to form a 0.1% DMSO solution as well.

[0877] Subsequently, the 24-well plate containing the incubated 3T3-L1 cells was withdrawn from the incubator. It was identified using a microscope that the cells became confluent, and the medium was removed through suction. 2 Wells of the 24-well plate were charged with the 0.1% DMSO solution in an amount of 1 ml/well, and the remaining 22

wells were charged with the solution of 1- μ M dexamethasone and 0.5mM IBMX in an amount of 1 ml/well. In this state, the incubation was conducted in an incubator at 37°C in 5% CO₂ for 1 day.

Preparation and addition of a test chemical agent and insulin

[0878] A test chemical agent was diluted with DMSO to 1 x 10⁻² M, 1 x 10⁻³ M and 1 x 10⁻⁴ M. The dilute solutions were further diluted to 500 times, and were adjusted to 2 X 10⁻⁵ M, 2 x 10⁻⁶ M and 2 x 10⁻⁷ M respectively. At the same time, a 0.2% DMSO solution was also prepared. Insulin which had been adjusted to 100 μ M (in 0.2% bovine serum albumin (BSA) and 3-mM HCl) and had been stored at -80°C was naturally thawed, diluted to 50,000 times with the medium, and adjusted to 2-nM.

[0879] Subsequently, the 24-well plate to which dexamethasone and IBMX had been added on the preceding day was withdrawn from the incubator. It was identified using a microscope that the shape of the cells was changed with the addition of dexamethasone and IBMX. Then, the medium was removed through suction. The 2 wells to which the 0.1% DMSO solution had been added on the preceding day were charged with the 0.2% DMSO solution in an amount of 500 μ l/well and the medium (this was required to check the cell state at that time). The remaining 22 wells (containing the solution of dexamethasone and IBMX) were charged with the 0.2% DMSO solution (2 wells) or the test chemical agent (20 wells) in an amount of 500 μ l/well and then with the insulin solution in an amount of 500 μ l/well. In this state, the incubation was conducted in an incubator at 37°C in 5% CO₂ for from 4 to 5 days.

Measurement of triglyceride (TG) and protein

[0880] Four to five days after the addition of the test chemical agent and the insulin solution, the 24-well plate was withdrawn from the incubator. The medium was discarded by decantation, and the remaining medium was then absorbed in a paper towel to completely remove the medium. Subsequently, the residue was extracted twice with isopropyl alcohol, and TG was measured at a wavelength of 410 nm using a TG-measuring kit (acetyl-acetone method). Subsequently, isopropyl alcohol was completely vaporized from the plate in which the extraction with isopropyl alcohol was completed. This plate was then charged with a 0.1-N NaOH solution in an amount of 400 μ l/well, and was allowed to stand at room temperature for 30 minutes to dissolve the cells. This solution was sampled into a tube in an amount of 50 μ l. Further, a solution obtained by diluting a Bio-Rad protein assay reagent to 5 times with distilled water was added to the tube in an amount of 2.5 ml. The mixture was stirred well, and protein was measured at a measurement wavelength of 595 nm using a spectrophotometer.

Results

[0881] The stimulatory activity of the test compound for TG accumulation was calculated, when 1 x 10⁻⁶ M of a control compound, pioglitazone, was defined as 100% and insulin (+) without the chemical agent was defined as 0%. The result is shown in the following.

Table 1

Concentration (M)	Stimulatory activity of TG accumulation (%)
1 x 10 ⁻⁵	38.2%

Test Example 2

[0882] Test for activity of decreasing plasma glucose using db/db mice

Test compounds

[0883]

6-benzenesulfonylcaramoyl-2-cyclopropyl-1-(2-fluorobenzyl)benzimidazole (177)

6-benzenesulfonylcaramoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole (163)

1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcaramoyl)-2-methylbenzimidazole (172)

Animal used

[0884] Five-week-old female mice [C57BL/KsJ-db+db+, C57BL/KsJ-db+ +m/+m (Jackson Laboratory)] were

purchased, and were kept for 2 to 3 weeks. Then, these mice were used in the test.

Preparation of an agent

5 [0885] A test compound was mixed with a powdered chow (CE-2, made by Nippon Clea) using a mortar. According to the amount of food intake of the mouse, the mixing ratios, 0.1%, 0.03%, and 0.01% corresponded to 100, 30, and 10 mg/kg body weight, respectively. The mixed chow was changed twice a week. The feed amount and the remaining amount were recorded, and the intake was calculated from the difference therebetween.

10 Test schedule

[0886] The female db/db mice were grouped according to the body weight, the plasma glucose and the plasma triglyceride concentrations. Then, the mixture containing the test compound was administered to the mice for 14 days (from 8 to 10 weeks old). In the morning on day 7 and day 14, the blood was collected from the orbital venous plexus using heparinized glass capillary tubes (Chase Heparinized Capillary Tubes), and a plasma fraction was obtained through centrifugal separation. Plasma glucose, triglyceride, and insulin concentrations were measured on day 0 and day 14 as well as plasma glucose and triglyceride concentrations on day 7. The body weight was measured on day 0, day 7, and day 14. After the final collection of the blood, the mice were killed using CO₂ gas.

20 Measurement method

[0887] The plasma glucose was measured by a glucose oxidase method (Glucose CII-Test Wako made by Wako Pure Chemical Industries, Ltd.) using from 10 to 15 µl of plasma. The plasma triglyceride concentration was measured by a GPO-p-chlorophenol method (Triglyceride G-Test Wako made by Wako Pure Chemical Industries, Ltd.) or a GPO-DAOS method (Triglyceride E-Test Wako) using from 10 to 15 µl of plasma. The above-mentioned measurements were conducted immediately after the blood collection. The plasma insulin concentration was measured by radio immuno assay method (Phadesef Insulin RIA Kit made by Cabi Pharmacia) using 20 µl of plasma (which can be stored at -20°C).

30 Results

[0888] The difference in the plasma glucose and the plasma triglyceride concentrations between the db/db mouse and the +/+ mouse was defined as 100%, and the rate (%) of decrease in the plasma glucose and the plasma triglyceride concentrations of the group to which the test compound was administered was calculated. The results were shown in Table 2.

Table 2

Compound No.	Dose (mg/kg)	Activity of decreasing plasma glucose (%)
(177)	30	34.5
(163)	30	72
(172)	10	70 - 80

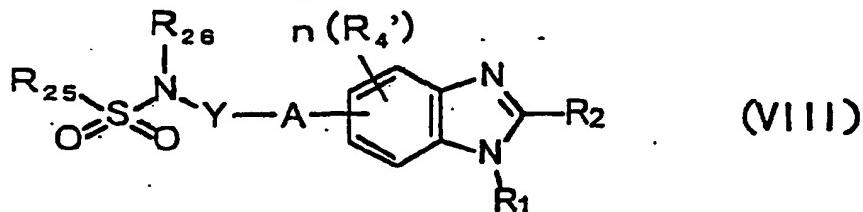
[0889] Herein provided are novel benzimidazole derivatives and their pharmaceutically acceptable salts. These compounds and their salts have blood sugar level-depressing activity or PDE5-inhibiting activity, and are useful for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobberling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, dia-

betic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

Claims

5

1. A benzimidazole derivative of the following formula, or its pharmaceutically acceptable salt:



wherein

20 R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyl group, an arylsulfonyl-lower alkyl group, an aryl-lower alkyl group, a haloaryl-lower alkyl group, an arylsulfonylamino group, an arylcarbonylamino group, an arylcarbonyl group, an arylalkenyl group, a cyanoaryl group, and a heterocyclic group, or by a heterocyclic group;

25 R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a hydroxy-lower alkyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a halocarbonyl group, an aryl group, or a heterocyclic group;

30 R_{25} represents an alkyl group having up to 8 carbon atoms, a lower cycloalkyl group, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

35 R_{26} represents a hydrogen atom or a lower alkyl group; provided that, when R_{25} and R_{26} are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group;

40 R_4' represents a hydrocarbon group or a halogenated hydrocarbon group; and
 n means an integer from 0 to 3;

wherein the arylsulfonyl group is selected from a benzenesulfonyl group, a toluenesulfonyl group, and a naphthalenesulfonyl group;

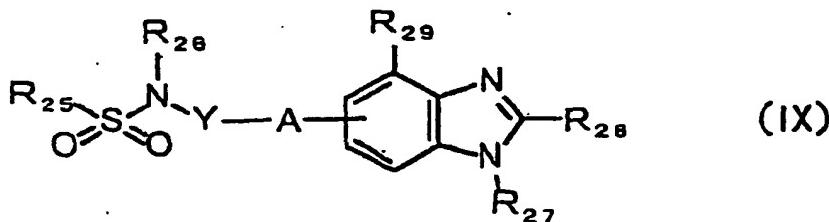
45 the term "lower" indicates that the group has from 1 to 6 carbon atoms, unless otherwise specifically indicated; the aryl group is selected from a phenyl group and a naphthyl group, which may optionally be substituted by one or more substituents selected from a halogen atom, a lower alkyl group, a cyano group, a nitro group and a trifluoromethyl group;

50 the halo-lower alkyl group is a linear or branched alkyl group having up to 8 carbon atoms, which is substituted with one or more halogen atoms;

55 the heterocyclic group is selected from a pyridyl group, a quinolyl group, an isoquirioly group, a thiazolyl group, a thiadiazolyl group, a benzofuranyl group, a dibenzofuranyl group, a thianaphthalenyl group, a 1H-1,2,3-triazolyl group, a 1,2,4-triazolyl group, a tetrazolyl group, a furyl group, a thieryl group, a pyrrolyl group, an imidazolyl group, a pyrimidinyl group, an indolyl group, a benzimidazolyl group, which groups may optionally be substituted by one or more substituents of halogen atoms and lower alkyl groups; and

the lower cycloalkyl group is a cycloalkyl group having from 3 to 7 carbon atoms.

2. A benzimidazole derivative according to claim 1 of the following formula, or its pharmaceutically acceptable salt:



10

wherein

R₂₇ represents a hydrogen atom, a lower alkyl group, an arylsulfonyl group or an aryl-lower alkyl group; wherein the aromatic ring moiety in said aryl-lower alkyl group may be substituted by one or two substituents selected from a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a heterocyclic group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

R₂₈ represents a hydrogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy-lower alkyl group, a lower cycloalkyl group, an aryl group, an aryl-lower alkyl group, a lower alkylamino group, a lower alkoxy group, a lower alkylthio group, a hydroxyl group, a mercapto group, an amino group, or a carboxyl group; R₂₅ represents an alkyl group having up to 8 carbon atoms, a halo-lower alkyl group, a tri-lower alkylsilyl-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkylthio-lower alkyl group, an aryl group, a heterocyclic group, an aryl-lower alkyl group, or a hydroxy-lower alkyl group; said aryl group may be substituted by a halogen atom, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, or a nitro group;

R₂₆ represents a hydrogen atom or a lower alkyl group; provided that, when R₂₅ and R₂₆ are both lower alkyl groups, they may be bonded together to form a ring;

Y represents a carbonyl group or a lower alkylene group;

A represents a single bond, or a lower alkylene or alkenylene group; and

R₂₉ represents a hydrogen atom or a lower alkyl group.

3. A pharmaceutical composition comprising a compound as claimed in claims 1 or 2 as an active ingredient.
- 35 4. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 2 , wherein R₂₇ represents an aryl-lower alkyl group whose aryl moiety may be substituted by one or two substituents selected from the group consisting of a halogen atom, a lower alkyl group, a halo-lower alkyl group, a cyanoaryl group, an amino group, a lower alkoxy group, a nitro group, a cyano group, an aryl group, a haloaryl group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, an aryl-lower alkyloxy group, an aryl-lower alkyl group, a heterocyclic group, an arylcarbonyl group, an arylcarbonylamino group, and an aryl-lower alkyloxy group substituted by one or two halogen atoms;

45 Y represents a carbonyl group; and

A represents a single bond.

5. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 4, wherein R₂₇ represents an aryl-lower alkyl group whose aryl moiety may be substituted by one or two substituents selected from a halogen atom or an aryl group;

50 R₂₈ represents a lower alkyl group or a lower cycloalkyl group;

R₂₅ represents an alkyl group having up to 8 carbon atoms or an aryl group;

Y represents a carbonyl group; and

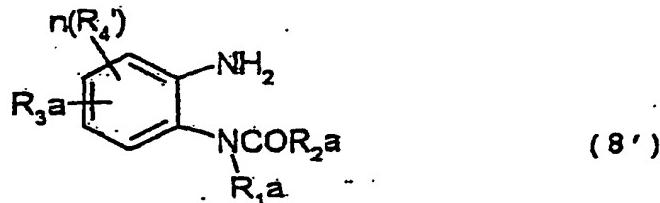
A represents a single bond.

- 55 6. The benzimidazole derivative or its pharmaceutically acceptable salt of claim 4 or 5, wherein said derivative is selected from the group consisting of 6-benzenesulfonylcarbamoyl-1-(2-chlorobenzyl)-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-methylbenzimidazole, 1-(biphenyl-4-ylmethyl)-6-(1-butanesulfonylcarbamoyl)-2-ethylbenzimidazole, 6-benzenesulfonylcarbamoyl-2-cyclopropyl-1-(2-fluorobenzyl)-

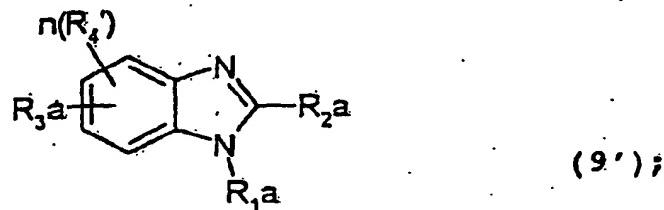
benzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-dichlorobenzyl)-2-methylbenzimidazole, 6-benzenesulfonylcarbamoyl-1-(2,4-difluorobenzyl)-2-methylbenzimidazole, 6-(1-butanesulfonylcarbamoyl)-1-[(3-fluorobiphenyl-4-yl)methyl]-2-methylbenzimidazole, 1-(2,4-dichlorobenzyl)-2-methyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole, and 1-(4-biphenylmethyl)-2-ethyl-6-(1-pentanesulfonylcarbamoyl)benzimidazole,

- 5
7. A pharmaceutical composition comprising a benzimidazole derivative or its pharmaceutically acceptable salt of any one of claims 4 to 6 and a pharmaceutically acceptable excipient.
 10. Use of a benzimidazole derivative or its pharmaceutically acceptable salt of any one of claims 1, 2 or 4 to 6 for preparing a pharmaceutical composition for preventing and treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases **characterized by** enteromotorility disorders, impotence, diabetic complications, nephritis, cancerous cachexia, or restenosis after PTCA.
 15. A method of producing a benzimidazole derivative or its pharmaceutically acceptable salt of any one of claims 1, 2 or 4 to 6, which comprises a step selected from the group consisting of steps (A), (B), (C), and (D):

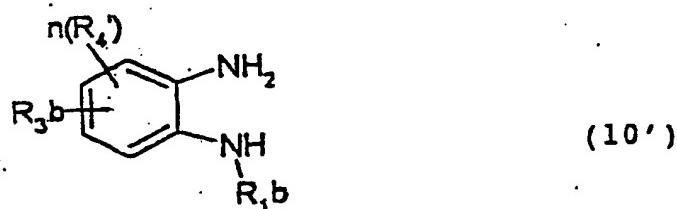
20 (A) effecting ring closure of a compound of the following formula (8'):



30 to give a benzimidazole derivative of the following formula (9'):

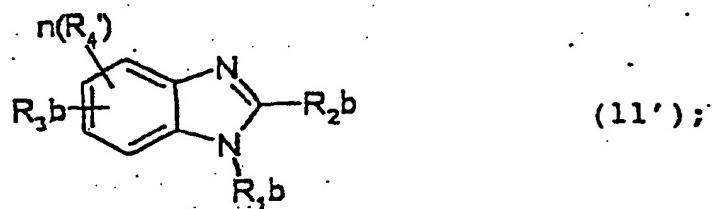


40 (B) reacting a compound of the following formula (10'):



50 with a carboxylic acid, acid halide, or acid anhydride having a substituent R2b to give a benzimidazole derivative of the following formula (11'):

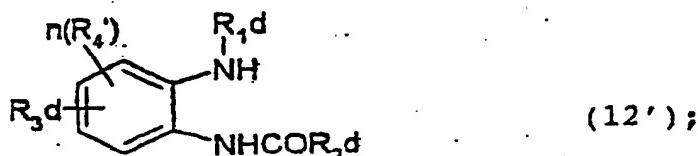
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(C) reacting a compound of the following formula (12'):

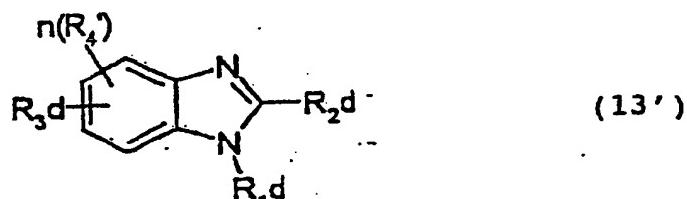
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with acid to give a benzimidazole derivative of the following formula (13'):

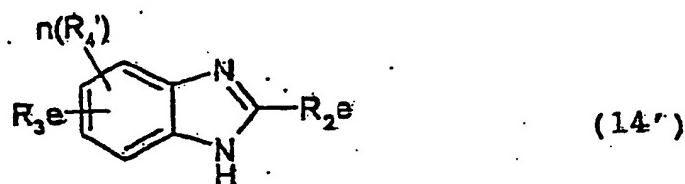
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(D) allowing a base to act on a compound of the following formula (14'):

35

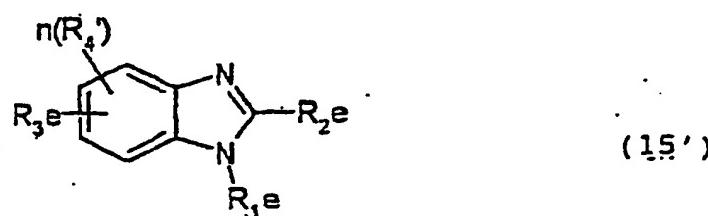


40

and reacting said compound with a compound represented by R_1eZ , wherein Z is a chlorine atom, a bromine atom, a toluenesulfonyloxy group, or a methanesulfonyloxy group, to give a benzimidazole derivative of the following formula (15'):

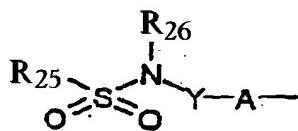
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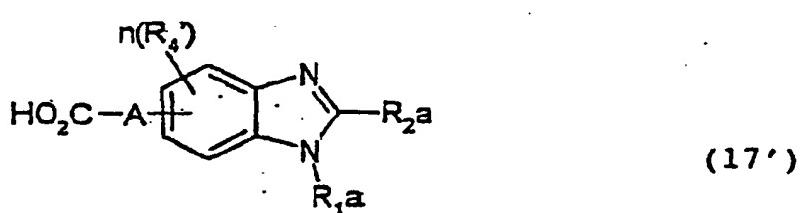
55

in the above formulae, R_1a to R_1e are R_1 or R_{27} , R_2a to R_2e are R_2 or R_{26} , R_3a to R_3e independently represent a substituent of the formula:

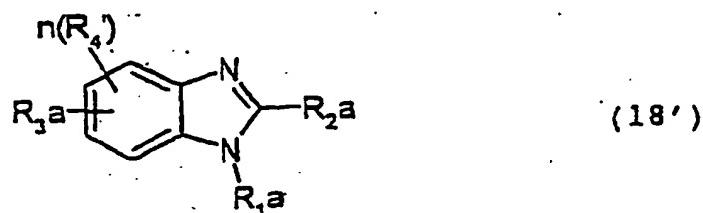


10 wherein R_{25} , R_{26} , Y and A have the same meaning as described above, R_4' has the same meaning as described above and includes the definition of R_{29} as described above, and n means an integer from 1 to 3.

- 15 10. A method of producing a benzimidazole derivative or its pharmaceutically acceptable salt of any one of claims 1, 2 or 4 to 6, wherein carbonyl diimidazole is allowed to act on a compound of the formula (17'),



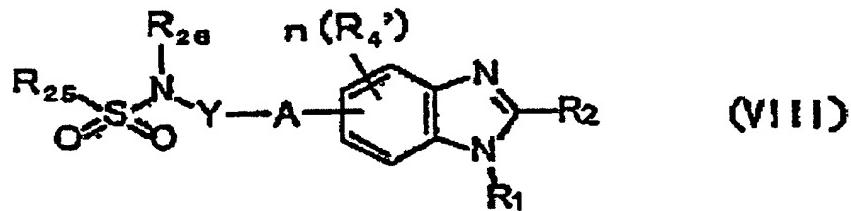
wherein R_1a , R_2a , R_4' , π , and A have the same meanings as described above, which is then reacted with amines and sulfonamides in the presence of a base to give a benzimidazole of the formula (18'):



wherein R_1a , R_2a , n , R_4' , and A have the same meanings as described above.

Patentansprüche

- 40 1. Benzimidazol-Derivat der folgenden Formel oder dessen pharmazeutisch verträgliches Salz:



wobei

55 R_1 ein Wasserstoffatom, einen Arylsulfonylrest oder einen Niederalkylrest bedeutet; der Niederalkylrest durch einen Arylrest oder einen mit einem oder zwei Substituenten, ausgewählt aus einem Halogenatom, einem Halogenarylrest, einem Niederalkylrest, einem Halogenniederalkylrest, einem Niederalkoxyrest, einer Nitrogruppe, einer Aminogruppe, einer Cyanogruppe, einem Arylrest, einem Arylniederalkyloxyrest, einem Arylsul-

fonylniederalkylrest, einem Arylniederalkylrest, einem Halogenarylniederalkyloxyrest, einem Arylsulfonylaminoest, einem Arylcarbonylaminorest, einem Arylcarbonylrest, einem Arylalkenylrest, einem Cyanoarylrest und einem heterocyclischen Rest, substituierten Arylrest oder durch einen heterocyclischen Rest substituiert sein kann;

R₂ ein Wasserstoffatom, einen Niedercycloalkylrest, eine Hydroxylgruppe, einen Hydroxyniederalkylrest, einen Niederalkoxyrest, eine Mercaptogruppe, einen Niederalkylthiorest, eine Aminogruppe, einen Niederalkylaminorest, eine Carboxylgruppe, einen Arylrest oder einen Niederalkylrest bedeutet; wobei der Niederalkylrest mit einem Halogenatom, einem Niederalkoxyrest, einer Cyanogruppe, einem Halogencarbonylrest, einem Arylrest oder einem heterocyclischen Rest substituiert sein kann;

R₂₅ einen Alkylrest mit bis zu 8 Kohlenstoffatomen, einen Niedercycloalkylrest, einen Halogenniederalkylrest, einen Triniederalkylsilylniederalkylrest, einen Niederalkoxyniederalkylrest, einen Niederalkylthioniederalkylrest, einen Arylrest, einen heterocyclischen Rest, einen Arylniederalkylrest oder einen Hydroxyniederalkylrest bedeutet; wobei der Arylrest mit einem Halogenatom, einem Niederalkylrest, einem Halogenniederalkylrest, einem Niederalkoxyrest oder einer Nitrogruppe substituiert sein kann;

R₂₆ ein Wasserstoffatom oder einen Niederalkylrest bedeutet;

mit der Maßgabe, dass, wenn R₂₅ und R₂₆ beide Niederalkylreste sind, diese unter Bildung eines Rings aneinander gebunden sein können;

Y einen Carbonylrest oder einen Niederalkylenrest bedeutet;

A eine Einfachbindung oder einen Niederalkylen- oder -alkenylenrest bedeutet;

R₄' einen Kohlenwasserstoffrest oder einen halogenierten Kohlenwasserstoffrest bedeutet; und

n eine ganze Zahl von 0 bis 3 bedeutet;

wobei der Arylsulfonylrest aus einem Benzolsulfonylrest, einem Toluolsulfonylrest und einem Naphthalinsulfonylrest ausgewählt ist;

der Ausdruck "Nieder" besagt, dass der Rest 1 bis 6 Kohlenstoffatome aufweist, sofern nicht konkret anders angegeben;

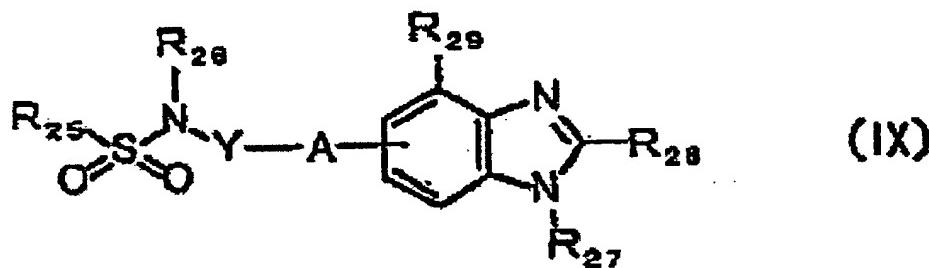
der Arylrest aus einem Phenylrest und einem Naphthylrest ausgewählt ist, die gegebenenfalls mit einem oder mehreren Substituenten, ausgewählt aus einem Halogenatom, einem Niederalkylrest, einer Cyanogruppe, einer Nitrogruppe und einer Trifluormethylgruppe, substituiert sein können;

der Halogenniederalkylrest ein linearer oder verzweigter Alkylrest mit bis zu 8 Kohlenstoffatomen ist, der mit einem oder mehreren Halogenatomen substituiert ist;

der heterocyclische Rest aus einer Pyridylgruppe, einer Chinolylgruppe, einer Isochinolylgruppe, einer Thiazolylgruppe, einer Thiadiazolylgruppe, einer Benzofuranylgruppe, einer Dibenzofuranylgruppe, einer Thianaphthalinylgruppe, einer 1H-1,2,3-Triazolylgruppe, einer 1,2,4-Triazolylgruppe, einer Tetrazolylgruppe, einer Furylgruppe, einer Thienylgruppe, einer Pyrrolylgruppe, einer Imidazolylgruppe, einer Pyrimidinylgruppe, einer Indolylgruppe, einer Benzimidazolylgruppe ausgewählt ist, wobei die Gruppen gegebenenfalls mit einem oder mehreren Substituenten aus Halogenatomen und Niederalkylresten substituiert sein können; und

der Niedercycloalkylrest ein Cycloalkylrest mit 3 bis 7 Kohlenstoffatomen ist.

2. Benzimidazol-Derivat nach Anspruch 1 der folgenden Formel oder dessen pharmazeutisch verträgliches Salz:



wobei

15 R₂₇ ein Wasserstoffatom, einen Niederalkylrest, einen Arylsulfonylrest oder einen Arylniederalkylrest bedeutet; wobei die aromatische Ringeinheit in dem Arylniederalkylrest mit einem oder zwei Substituenten, ausgewählt aus einem Halogenatom, einem Niederalkylrest, einem Halogenniederalkylrest, einem Cyanoarylrest, einer Aminogruppe, einem Niederalkoxyrest, einer Nitrogruppe, einer Cyanogruppe, einem Arylrest, einem Halogenarylrest, einem Arylsulfonylniederalkylrest, einem Arylsulfonylaminorest, einem Arylniederalkyloxyrest, einem Arylniederalkylrest, einem heterocyclischen Rest, einem Arylcarbonylrest, einem Arylcarbonylaminorest und einem Arylniederalkyloxyrest, substituiert mit einem oder zwei Halogenatomen, substituiert sein kann;

20

25 R₂₈ ein Wasserstoffatom, einen Niederalkylrest, einen Halogenniederalkylrest, einen Niederalkoxyniederalkylrest, einen Niedercycloalkylrest, einen Arylrest, einen Arylniederalkylrest, einen Niederalkylaminorest, einen Niederalkyloxyrest, einen Niederalkylthiorest, eine Hydroxylgruppe, eine Mercaptogruppe, eine Aminogruppe oder eine Carboxylgruppe bedeutet;

30

35 R₂₅ einen Alkylrest mit bis zu 8 Kohlenstoffatomen, einen Halogenniederalkylrest, einen Triniederalkylsilylniederalkylrest, einen Niederalkoxyniederalkylrest, einen Niederalkylthioniederalkylrest, einen Arylrest, einen heterocyclischen Rest, einen Arylniederalkylrest oder einen Hydroxyniederalkylrest bedeutet; wobei der Arylrest mit einem Halogenatom, einem Niederalkylrest, einem Halogenniederalkylrest, einem Niederalkyloxyrest oder einer Nitrogruppe substituiert sein kann;

R₂₆ ein Wasserstoffatom oder einen Niederalkylrest bedeutet;

40

45 mit der Maßgabe, dass, wenn R₂₅ und R₂₆ beide Niederalkylreste sind, diese unter Bildung eines Rings aneinander gebunden sein können;

Y einen Carbonylrest oder einen Niederalkylenrest bedeutet;

A eine Einfachbindung oder einen Niederalkylen- oder -alkenylenrest bedeutet; und

R₂₉ ein Wasserstoffatom oder einen Niederalkylrest bedeutet.

- 45 3. Arzneimittel umfassend eine Verbindung nach den Ansprüchen 1 oder 2 als Wirkstoff.
- 50 4. Benzimidazol-Derivat oder dessen pharmazeutisch verträgliches Salz nach Anspruch 2, wobei R₂₇ einen Arylniederalkylrest bedeutet, dessen Aryleinheit mit einem oder zwei Substituenten, ausgewählt aus einem Halogenatom, einem Niederalkylrest, einem Halogenniederalkylrest, einem Cyanoarylrest, einer Aminogruppe, einem Niederalkoxyrest, einer Nitrogruppe, einer Cyanogruppe, einem Arylrest, einem Halogenarylrest, einem Arylsulfonylniederalkylrest, einem Arylsulfonylaminorest, einem Arylniederalkyloxyrest, einem Arylniederalkylrest, einem heterocyclischen Rest, einem Arylcarbonylrest, einem Arylcarbonylaminorest und einem Arylniederalkyloxyrest, substituiert mit einem oder zwei Halogenatomen, substituiert sein kann;

55

55 Y einen Carbonylrest bedeutet; und

A eine Einfachbindung bedeutet.

5. Benzimidazol-Derivat oder dessen pharmazeutisch verträgliches Salz nach Anspruch 4, wobei R₂₇ einen Arylniederalkylrest bedeutet, dessen Aryleinheit mit einem oder zwei Substituenten, ausgewählt aus einem Halogenatom oder einem Arylrest, substituiert sein kann;

5 R₂₈ einen Niederalkylrest oder einen Niedercycloalkylrest bedeutet;

R₂₅ einen Alkylrest mit bis zu 8 Kohlenstoffatomen oder einen Arylrest bedeutet;

10 Y einen Carbonylrest bedeutet; und

15 A eine Einfachbindung bedeutet.

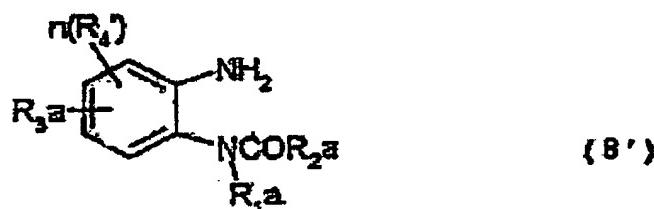
6. Benzimidazol-Derivat oder dessen pharmazeutisch verträgliches Salz nach Anspruch 4 oder 5, wobei das Derivat ausgewählt ist aus 6-Benzolsulfonylcaramoyl-1-(2-chlorbenzyl)-2-methylbenzimidazol, 1-(Biphenyl-4-ylmethyl)-6-(1-butansulfonylcaramoyl)-2-methylbenzimidazol, 1-(Biphenyl-4-ylmethyl)-6-(1-butansulfonylcaramoyl)-2-ethylbenzimidazol, 6-Benzolsulfonylcaramoyl-2-cyclopropyl-1-(2-fluorbenzyl)-benzimidazol, 6-Benzolsulfonylcaramoyl-1-(2,4-dichlor-benzyl)-2-methylbenzimidazol, 6-Benzolsulfonylcaramoyl-1-(2,4-difluorbenzyl)-2-methylbenzimidazol, 6-(1-Butansulfonylcaramoyl)-1-[(3-fluorbiphenyl-4-yl)methyl]-2-methylbenzimidazol, 1-(2,4-Dichlorbenzyl)-2-methyl-6-(1-pentansulfonylcaramoyl)benzimidazol und 1-(4-Biphenylmethyl)-2-ethyl-6-(1-pentan-sulfonylcaramoyl)benzimidazol.

7. Arzneimittel umfassend ein Benzimidazol-Derivat oder dessen pharmazeutisch verträgliches Salz nach einem der Ansprüche 4 bis 6 und einen pharmazeutisch verträglichen Exzipienten.

- 25 8. Verwendung eines Benzimidazol-Derivats oder des pharmazeutisch verträglichen Salzes desselben nach einem der Ansprüche 1, 2 oder 4 bis 6 zur Herstellung eines Arzneimittels zur Prävention und Behandlung von beeinträchtigter Glucosetoleranz, Diabetes, diabetischen Komplikationen, dem Syndrom der Insulinresistenz, Hyperlipidämie, Atherosklerose, Herz-Kreislauf-Störungen, Hyperglykämie oder Hypertonie; oder Stenokardie, Hypertonie, pulmonaler Hypertonie, kongestiver Herzinsuffizienz, Glomerulopathie, tubulointerstitiellen Störungen, Nierenversagen, Atherosklerose, Angiostenose, distaler Angiopathie, Schlaganfall, chronischen reversiblen Obstruktionen, allergischer Rhinitis, Urticaria, Glaukom, Erkrankungen, die durch Enteromotilitätsstörungen gekennzeichnet sind, Impotenz, diabetischen Komplikationen, Nephritis, Kachexie bei Malignomerkrankung oder Restenose nach PTCA.

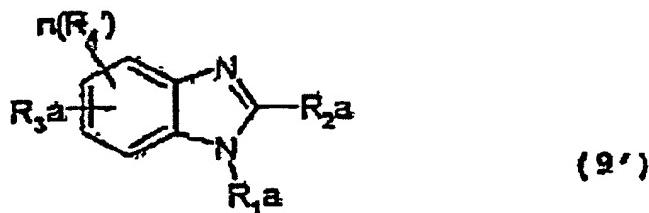
- 35 9. Verfahren zur Herstellung eines Benzimidazol-Derivats oder des pharmazeutisch verträglichen Salzes desselben nach einem der Ansprüche 1, 2 oder 4 bis 6, welches einen Schritt umfasst, der ausgewählt ist aus den Schritten (A), (B), (C) und (D):

(A) Durchführen eines Ringschlusses einer Verbindung der folgenden Formel (8'):



50 um ein Benzimidazol-Derivat der folgenden Formel (9') zu ergeben:

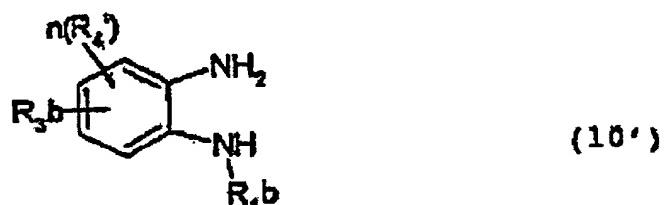
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(B) Umsetzen einer Verbindung der folgenden Formel (10'):

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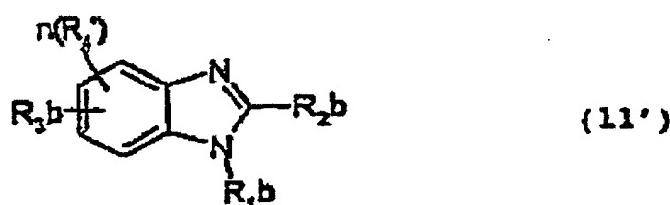


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mit einer Carbonsäure, einem Säurehalogenid oder einem Säureanhydrid mit einem Substituenten R₂b, um ein Benzimidazol-Derivat der folgenden Formel (11') zu ergeben:

25

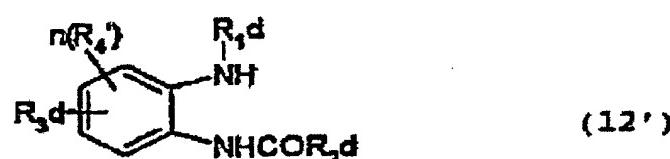
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(C) Umsetzen einer Verbindung der folgenden Formel (12'):

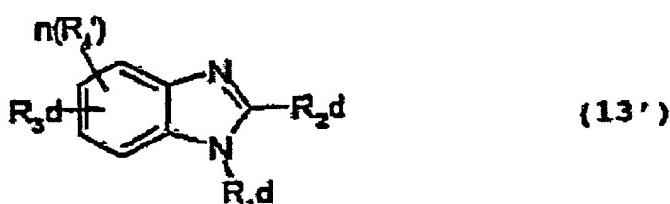
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mit Säure, um ein Benzimidazol-Derivat der folgenden Formel (13') zu ergeben:

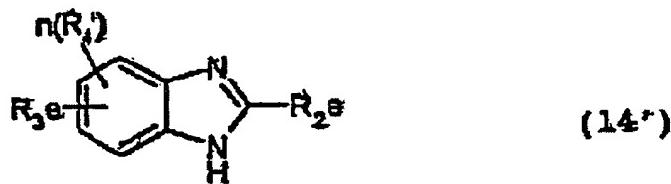
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(D) Einwirkenlassen einer Base auf eine Verbindung der folgenden Formel (14'):

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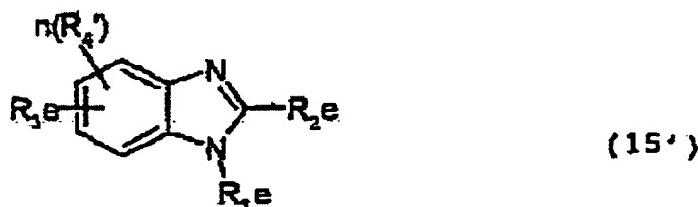


10 und Umsetzen der Verbindung mit einer durch R_1eZ dargestellten Verbindung, wobei Z ein Chloratom, ein Bromatom, eine Toluolsulfonyloxygruppe oder eine Methansulfonyloxygruppe ist, um ein Benzimidazol-Derivat der folgenden Formel (15') zu ergeben:

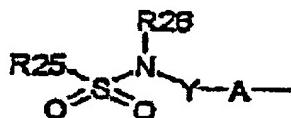
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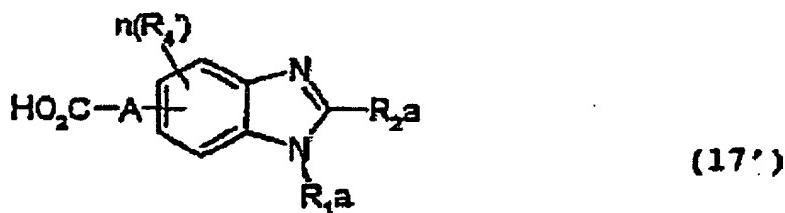


35 darstellen, wobei R_{25} , R_{26} , Y und A die gleiche Bedeutung wie oben beschrieben haben, R_4' die gleiche Bedeutung wie oben beschrieben hat und die Definition von R_{29} wie oben beschrieben beinhaltet, und n eine ganze Zahl von 1 bis 3 bedeutet.

40 10. Verfahren zur Herstellung eines Benzimidazol-Derivats oder des pharmazeutisch verträglichen Salzes desselben nach einem der Ansprüche 1, 2 oder 4 bis 6, wobei man Carboonyldiimidazol auf eine Verbindung der Formel (17') einwirken lässt,

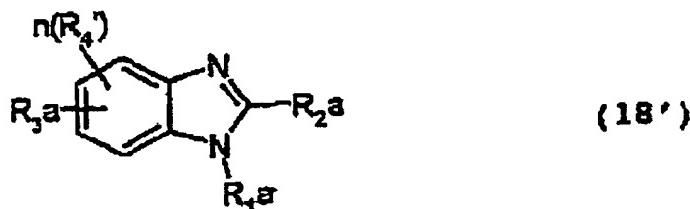
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wobei R_1a , R_2a , R_4' , n und A die gleichen Bedeutungen wie oben beschrieben haben, welche dann mit Aminen und Sulfonamiden in Gegenwart einer Base umgesetzt wird, um ein Benzimidazol der Formel (18') zu ergeben:

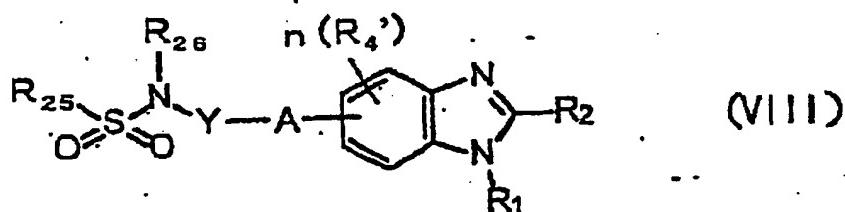
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10 wobei R₁a, R₂a, n, R₄' und A die gleichen Bedeutungen wie oben beschrieben haben.

Revendications

- 15 1. Dérivé de benzimidazole de formule suivante, ou son sel acceptable du point de vue pharmaceutique :



dans laquelle

- 30 R₁ représente un atome d'hydrogène, un groupe arylsulfonyle, ou un groupe alkyle inférieur; ledit groupe alkyle inférieur peut être substitué par un groupe aryle ou un groupe aryle substitué par un ou deux substituants choisis parmi un atome d'halogène, un groupe haloaryle, un groupe alkyle inférieur, un groupe halo- alkyle inférieur, un groupe alkoxy inférieur, un groupe nitro, un groupe amino, un groupe cyano, un groupe aryle, un groupe aryl- alkylxy inférieur, un groupe arylsulfonyl- alkyle inférieur, un groupe aryl- alkyle inférieur, un groupe haloaryl-alkylxy inférieur, un groupe arylsulfonylamino, un groupe arylcarbonylamino, un groupe arylcarbonyle, un groupe arylalcényle, un groupe cyanoaryle, et un groupe hétérocyclique, ou par un groupe hétérocyclique ;
- 35 R₂ représente un atome d'hydrogène, un groupe cycloalkyle inférieur, un groupe hydroxy, un groupe hydroxy- alkyle inférieur, un groupe alkoxy inférieur, un groupe mercapto, un groupe alkylthio inférieur, un groupe amino, un groupe alkylamino inférieur, un groupe carboxy, un groupe aryle, ou un groupe alkyle inférieur ; ledit groupe alkyle inférieur peut être substitué par un atome d'halogène, un groupe alkoxy inférieur, un groupe cyano, un groupe halocarbonyle, un groupe aryle, ou un groupe hétérocyclique ;
- 40 R₂₅ représente un groupe alkyle possédant jusqu'à 8 atomes de carbone, un groupe cycloalkyle inférieur, un groupe halo- alkyle inférieur, un groupe tri-alkyle silyl- alkyle inférieur, un groupe alkoxy inférieur- alkyle inférieur, un groupe alkyl inférieur thio- alkyle inférieur, un groupe aryle, un groupe hétérocyclique, un groupe aryl- alkyle inférieur, ou un groupe hydroxy- alkyle inférieur ; ledit groupe aryle peut être substitué par un atome d'halogène, un groupe alkyle inférieur, un groupe halo- alkyle inférieur, un groupe alkoxy inférieur, ou un groupe nitro ;
- 45 R₂₆ représente un atome d'hydrogène ou un groupe alkyle inférieur; étant entendu que lorsque R₂₅ et R₂₆ représentent tous les deux à la fois des groupes alkyle inférieurs, ils peuvent être reliés ensemble pour former un cycle ;
- 50 Y représente un groupe carbonyle ou un groupe alkylène inférieur ;
- A représente une liaison simple, ou un groupe alkylène ou alcénylène inférieur ;
- 55 R₄' représente un groupe hydrocarbure ou un groupe hydrocarbure halogéné ; et n signifie un nombre entier de 0 à 3 ;

dans laquelle le groupe arylsulfonyle est choisi parmi un groupe benzènesulfonyle, un groupe toluènesulfonyle, et un groupe naphtalènesulfonyle ;

le terme "inférieur" indique que le groupe possède de 1 à 6 atomes de carbone, sauf indication spécifique contraire ;

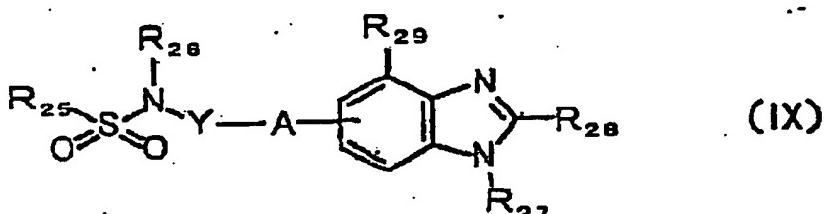
le groupe aryle est choisi parmi un groupe phényle et un groupe naphtyle, qui peuvent éventuellement être substitués par un ou plusieurs substituants choisis parmi un atome d'halogène, un groupe alkyle inférieur, un groupe cyano, un groupe nitro et un groupe trifluorométhyle ;

le groupe halo- alkyle inférieur est un groupe alkyle linéaire ou ramifié possédant jusqu'à 8 atomes de carbone, qui est substitué par un ou plusieurs atomes d'halogène ;

le groupe hétérocyclique est choisi parmi un groupe pyridyle, un groupe quinolyle, un groupe isoquinolyle, un groupe thiazolyle, un groupe thiadiazolyle, un groupe benzofuranyle, un groupe dibenzofuranylé, un groupe thianaphthalényle, un groupe 1H-1,2,3-triazolyle, un groupe 1,2,4-triazolyle, un groupe tétrazolyle, un groupe furyle, un groupe thiényle, un groupe pyrrolyle, un groupe imidazolyle, un groupe pyrimidinyle, un groupe indolyle, un groupe benzimidazolyle, lesquels groupes peuvent éventuellement substitués par un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieurs ; et

le groupe cycloalkyle inférieur est un groupe cycloalkyle possédant de 3 à 7 atomes de carbone.

- 15 2. Dérivé de benzimidazole selon la revendication 1 de formule suivante, ou son sel acceptable du point de vue pharmaceutique:



20 dans laquelle

25 R₂₇ représente un atome d'hydrogène, un groupe alkyle inférieur, un groupe arylsulfonyle ou un groupe aryl- alkyle inférieur ; dans laquelle l'entité noyau aromatique dans ledit groupe aryl- alkyle inférieur peut être substituée par un ou deux substituants choisis parmi un atome d'halogène, un groupe alkyle inférieur, un groupe halo- alkyle inférieur, un groupe cyanoaryle, un groupe amino, un groupe alkoxy inférieur, un groupe nitro, un groupe cyano, un groupe aryle, un groupe haloaryle, un groupe arylsulfonyl- alkyle inférieur, un groupe arylsulfonylamino, un groupe aryl- alkyloxy inférieur, un groupe aryl- alkyle inférieur, un groupe hétérocyclique, un groupe arylcarbonyle, un groupe arylcarbonylamino, et un groupe aryl- alkyloxy inférieur substitué par un ou deux atomes d'halogène ;

30 R₂₈ représente un atome d'hydrogène, un groupe alkyle inférieur, un groupe halo- alkyle inférieur, un groupe alkoxy inférieur- alkyle inférieur, un groupe cycloalkyle inférieur, un groupe aryle, un groupe aryl- alkyle inférieur, un groupe alkylamino inférieur, un groupe alkoxy inférieur, un groupe alkylthio inférieur, un groupe hydroxy, un groupe mercapto, un groupe amino, ou un groupe carboxy ;

35 R₂₅ représente un groupe alkyle possédant jusqu'à 8 atomes de carbone, un groupe halo- alkyle inférieur, un groupe tri-alkyle inférieur silyl- alkyle inférieur, un groupe alkoxy inférieur- alkyle inférieur, un groupe alkyle inférieur thio- alkyle inférieur, un groupe aryle, un groupe hétérocyclique, un groupe aryl- alkyle inférieur, ou un groupe hydroxy- alkyle inférieur ; ledit groupe aryle peut être substitué par un atome d'halogène, un groupe alkyle inférieur, un groupe halo- alkyle inférieur, un groupe alkoxy inférieur, ou un groupe nitro ;

40 R₂₆ représente un atome d'hydrogène ou un groupe alkyle inférieur ; étant entendu que lorsque R₂₅ et R₂₆ représentent tous les deux des groupes alkyle inférieurs, ils peuvent reliés ensemble pour former un cycle ;

45 Y représente un groupe carbonyle ou un groupe alkylène inférieur ; et

50 A représente une liaison simple, ou un groupe alkylène ou alcénylène inférieur ; et

R₂₉ représente un atome d'hydrogène ou un groupe alkyle inférieur.

- 55 3. Composition pharmaceutique comprenant un composé selon la revendication 1 ou 2 à titre d'ingrédient actif.
4. Dérivé de benzimidazole ou son sel acceptable du point de vue pharmaceutique selon la revendication 2, dans lequel R₂₇ représente un groupe aryl-alkyle inférieur dont l'entité aryle peut être substituée par un ou deux substituants choisis dans le groupe consistant en un atome d'halogène, un groupe alkyle inférieur, un groupe halo-

alkyle inférieur, un groupe cyanoaryl, un groupe amino, un groupe alkoxy inférieur, un groupe nitro, un groupe cyano, un groupe aryle, un groupe haloaryl, un groupe arylsulfonyl- alkyle inférieur, un groupe arylsulfonylamino, un groupe aryl- alkylxy inférieur, un groupe aryl- alkyle inférieur, un groupe hétérocyclique, un groupe arylcarbonyl, un groupe arylcarbonylamino, et un groupe aryl- alkylxy inférieur substitué par un ou deux atomes d'halogène ;

Y représente un groupe carbonyle ; et
A représente une liaison simple.

- 5 10 5. Dérivé de benzimidazole ou son sel acceptable du point de vue pharmaceutique selon la revendication 4, dans lequel R₂₇ représente un groupe aryl-alkyle inférieur dont l'entité aryle peut être substituée par un ou deux substituants choisis parmi un atome d'halogène ou un groupe aryle ;

R₂₈ représente un groupe alkyle inférieur ou un groupe cycloalkyle inférieur ;
R₂₅ représente un groupe alkyle possédant jusqu'à 8 atomes de carbone ou un groupe aryle ;
Y représente un groupe carbonyle ; et
A représente une liaison simple.

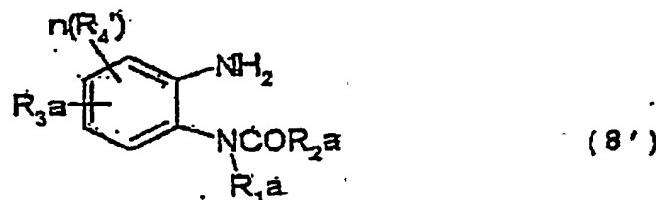
- 20 25 6. Dérivé de benzimidazole ou son sel acceptable du point de vue pharmaceutique selon la revendication 4 ou 5, dans lequel ledit dérivé est choisi dans le groupe consistant en 6-benzènesulfonylcarbamoyl -1-(2-chlorobenzyl) -2-méthyl benzimidazole, 1-(biphényl-4-ylméthyl) -6-(1-butanesulfonylcarbamoyl) -2-méthyl benzimidazole, 1-(biphényl-4-ylméthyl) -6-(1-butanesulfonylcarbamoyl) -2-éthyl benzimidazole, 6-benzènesulfonylcarbamoyl -2-cyclopropyl -1-(2-fluorobenzyl) benzimidazole, 6-benzènesulfonylcarbamoyl -1-(2,4-dichlorobenzyl) -2-méthyl benzimidazole, 6-benzènesulfonylcarbamoyl -1-(2,4-difluorobenzyl) -2-méthyl benzimidazole, 6-(1-butanesulfonylcarbamoyl) -1-[(3-fluorobiphényl-4-yl) méthyl] -2-méthyl benzimidazole, 1-(2,4-dichlorobenzyl) -2-méthyl -6-(1-pentanesulfonylcarbamoyl) benzimidazole, et 1-(4-biphénylméthyl) -2-éthyl -6-(1-pentanesulfonylcarbamoyl) benzimidazole.

- 30 7. Composition pharmaceutique comprenant un dérivé de benzimidazole ou son sel acceptable du point de vue pharmaceutique selon l'une quelconque des revendications 4 à 6 et un excipient acceptable du point de vue pharmaceutique.

- 35 40 8. Utilisation d'un dérivé de benzimidazole ou de son sel acceptable du point de vue pharmaceutique selon l'une quelconque des revendications 1, 2 ou 4 à 6 pour la préparation d'une composition pharmaceutique pour la prévention et le traitement de tolérance au glucose réduite, diabète, complications diabétiques, syndrome dé résistance à l'insuline, hyperlipidémie, athérosclérose, troubles cardiovasculaires, hyperglycémie ou hypertension ; ou sténocardie, hypertension, hypertension pulmonaire, insuffisance cardiaque congestive, glomérulopathie, troubles tubulointerstitiels, insuffisance rénale, athérosclérose, angio-sténose, angiopathie distale, apoplexie cérébrale, obstructions chroniques réversibles, rhinite allergique, urticaire, glaucome, maladies **caractérisées par** des troubles d'entéromotilité, impotence, complications diabétiques, néphrite, cachexie tumorale, ou resténose après PT-CA.

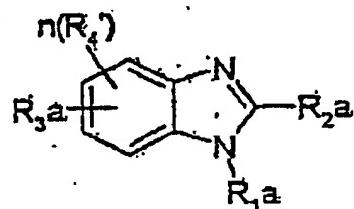
- 45 9. Procédé de production d'un dérivé de benzimidazole ou de son sel acceptable du point de vue pharmaceutique selon l'une quelconque des revendications 1, 2 ou 4 à 6, qui comprend une étape choisie dans le groupe consistant en les étapes (A), (B), (C), et (D) :

(A) réalisation d'une fermeture de cycle sur un composé de formule suivante (8') :



pour donner un dérivé de benzimidazole de formule suivante (9') :

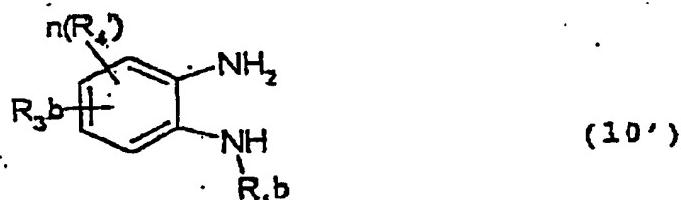
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(B) mise en réaction d'un composé de formule suivante (10') :

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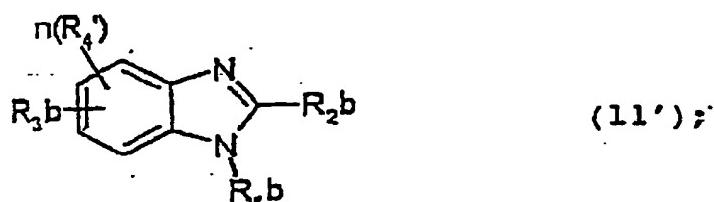


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avec un acide carboxylique, un halogénure d'acide, ou un anhydride d'acide possédant un substituant R2b pour donner un dérivé de benzimidazole de formule suivante (11') :

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(C) mise en réaction d'un composé de formule suivante (12') :

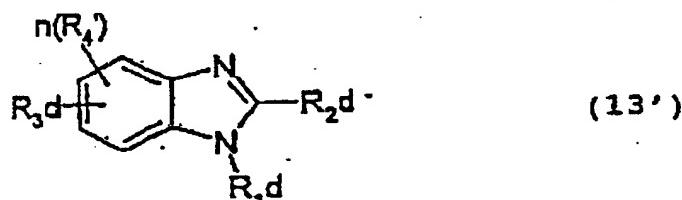
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avec un acide pour donner un dérivé de benzimidazole de formule suivante (13') :

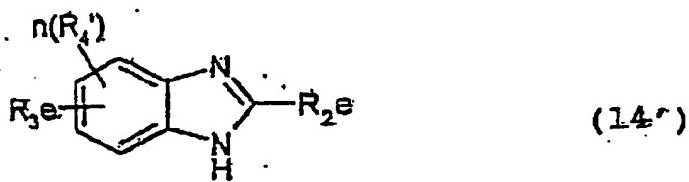
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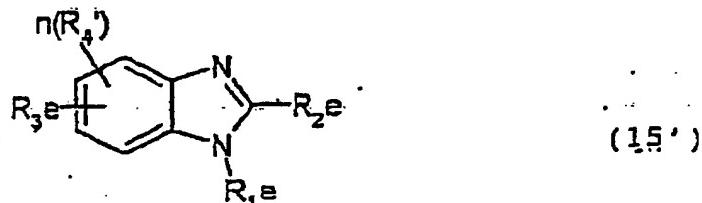
(D) permettre une base d'agir sur un composé de formule suivante (14') :

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et réaction dudit composé avec un composé représenté par R_1eZ , dans lequel Z est un atome de chlore, un atome de brome, un groupe toluènesulfonyloxy, ou un groupe méthanesulfonyloxy, pour donner un dérivé de benzimidazole de formule suivante (15') :

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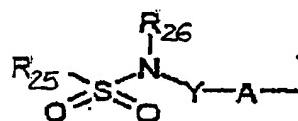


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dans les formules ci-dessus, R_1a à R_1e sont R_1 ou R_{27} , R_2a à R_2e sont R_2 ou R_{28} , R_3a à R_3e représentent indépendamment un substituant de formule :

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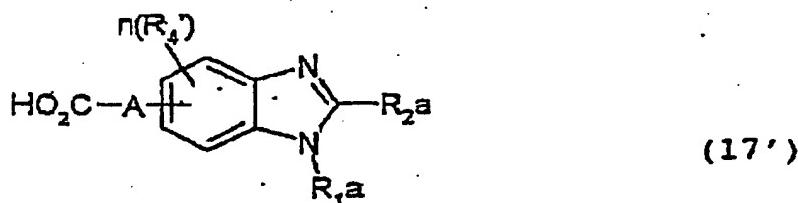


dans laquelle R_{25} , R_{26} , Y et A possèdent les mêmes significations que décrit ci-dessus, R_4' possède la même signification que décrit ci-dessus et comprend la définition de R_{29} comme décrit ci-dessus, et n signifie un nombre entier de 1 à 3.

10. Procédé de production d'un dérivé de benzimidazole ou de son sel acceptable du point de vue pharmaceutique selon l'une quelconque des revendications 1, 2 ou 4 à 6, dans lequel on permet un carbonyliimidazole d'agir sur un composé de formule (17'):

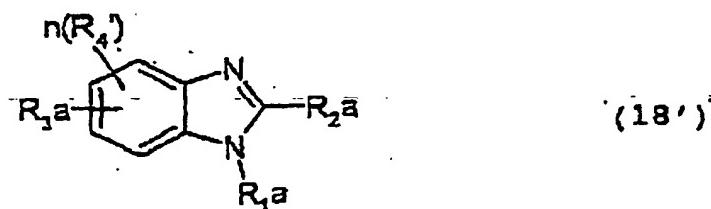
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50 dans laquelle R_1a , R_2a , R_4' , n, et A possèdent les mêmes significations que décrit ci-dessus, puis est ensuite mis en réaction avec des amines et sulfonamides en présence d'une base pour donner un benzimidazole de formule (18'):

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dans laquelle R₁a, R₂a, n, R₄', et A possèdent les mêmes significations que décrit ci-dessus.

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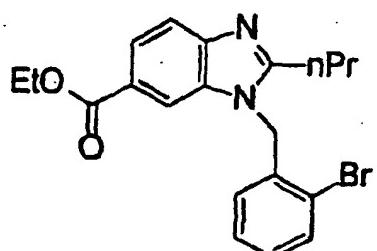
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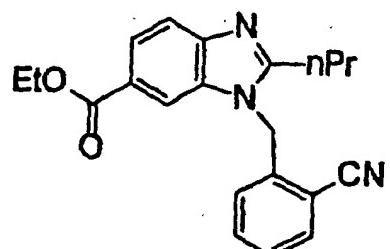
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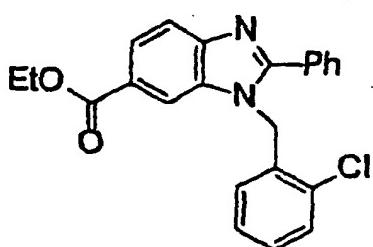
FIG. 1



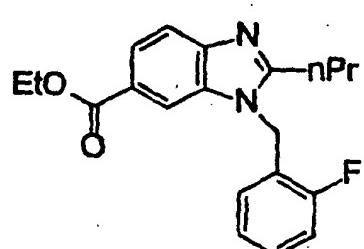
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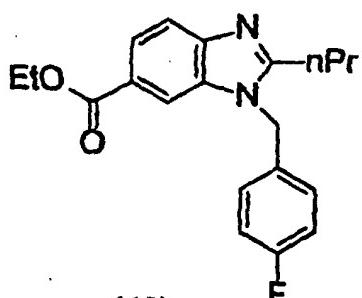
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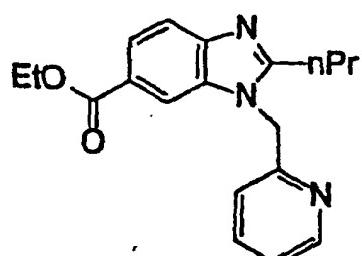
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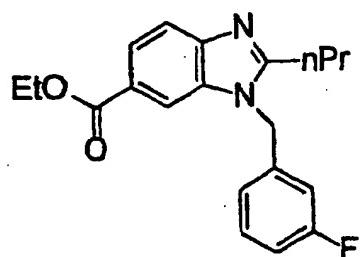


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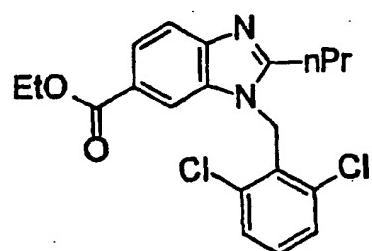


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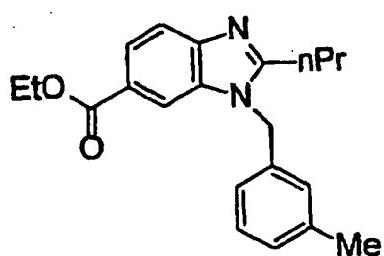
F I G . 2



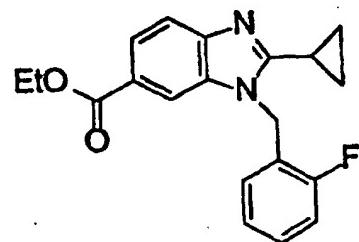
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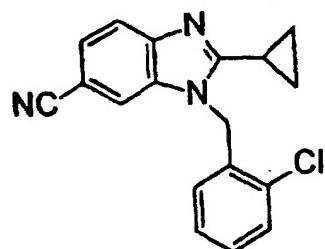
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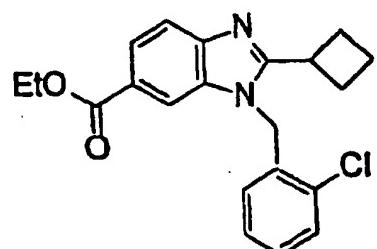
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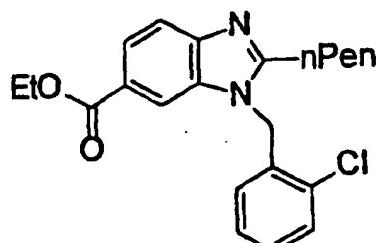


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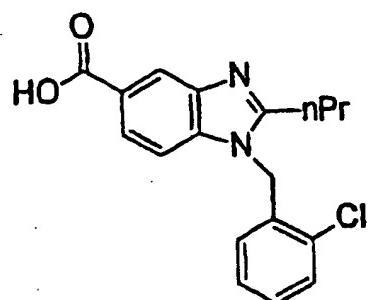


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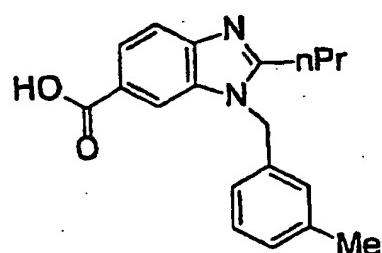
F I G . 3



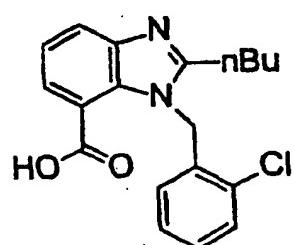
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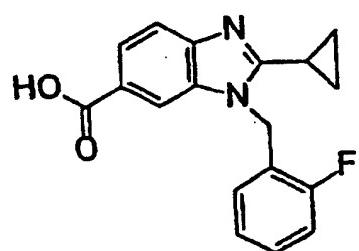
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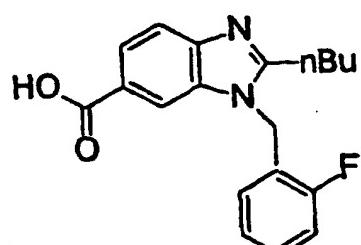
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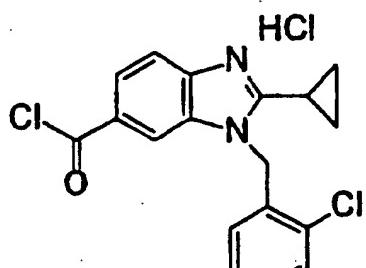


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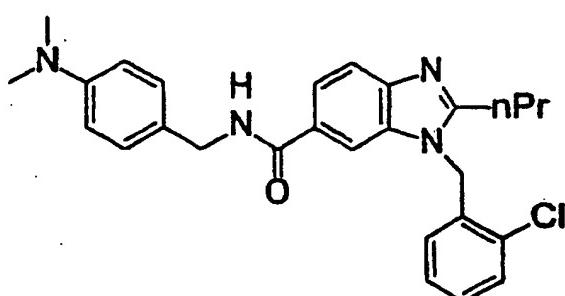


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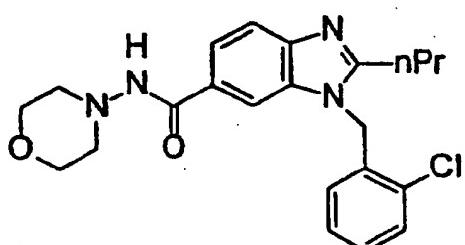
FIG. 4



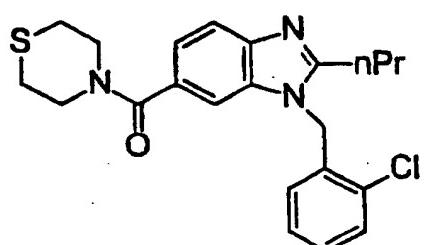
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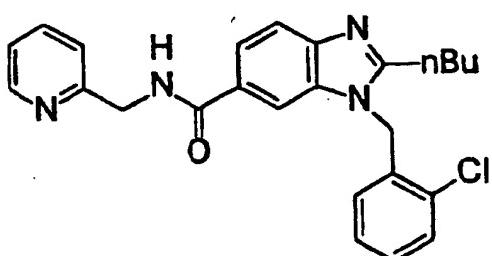
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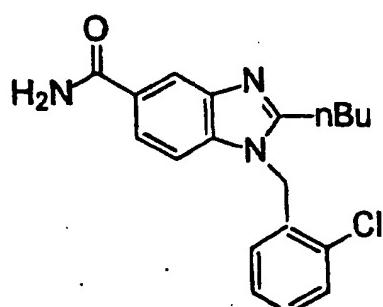
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(63)

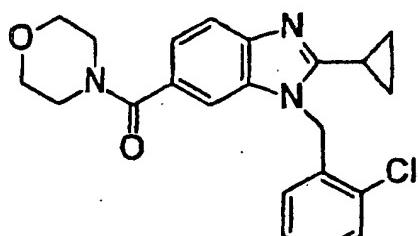


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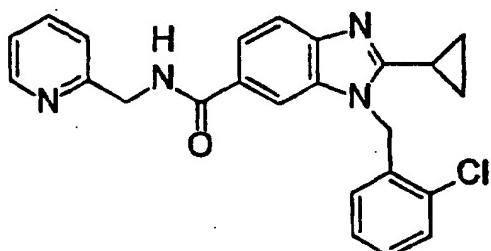


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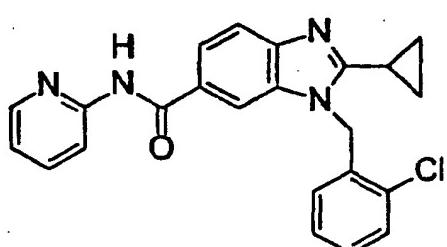
FIG. 5



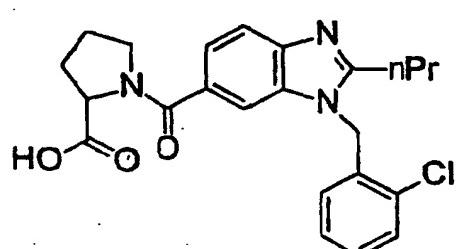
(66)



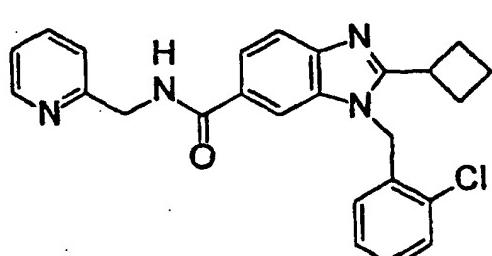
(67)



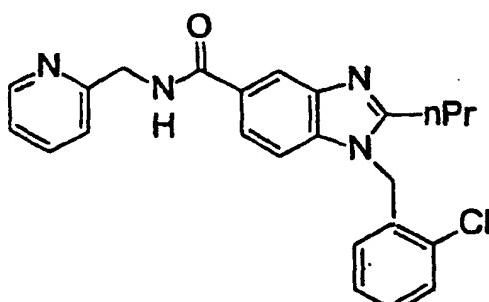
(68)



(69)

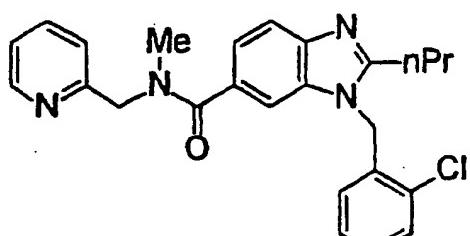


(70)

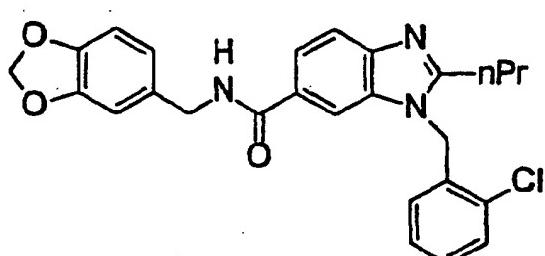


(71)

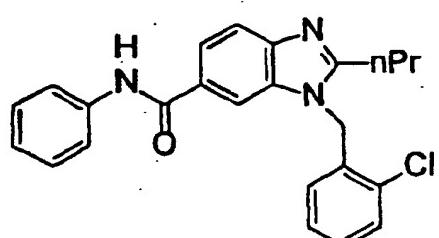
FIG. 6



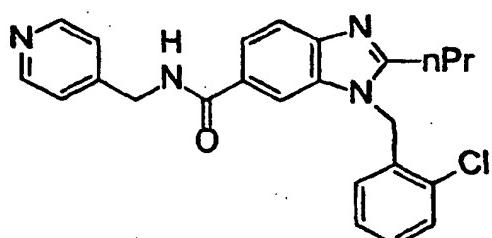
(72)



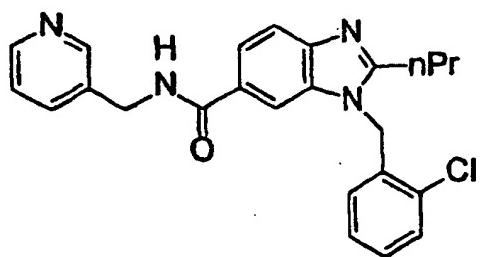
(73)



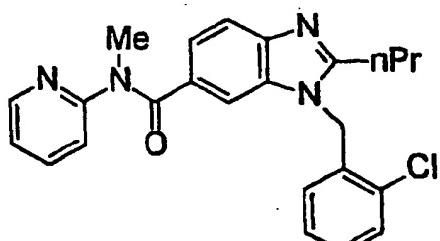
(74)



(75)

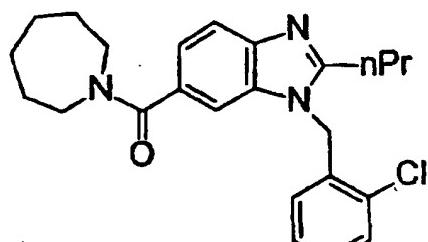


(76)

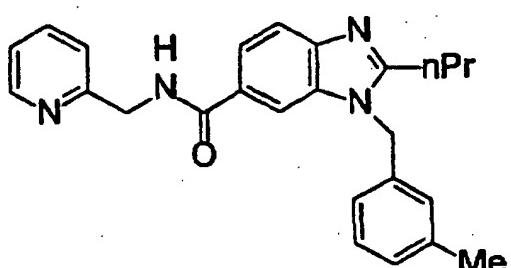


(77)

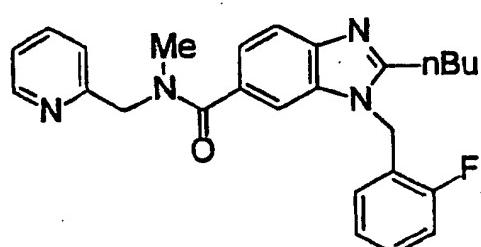
FIG. 7



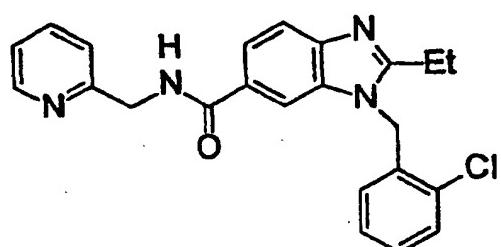
(78)



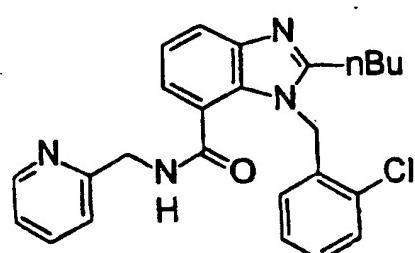
(79)



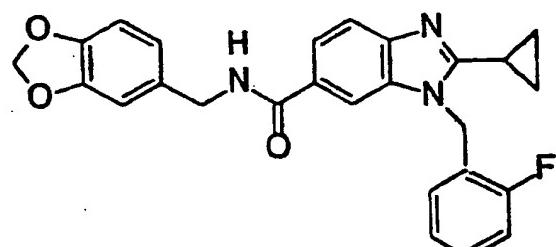
(80)



(81)

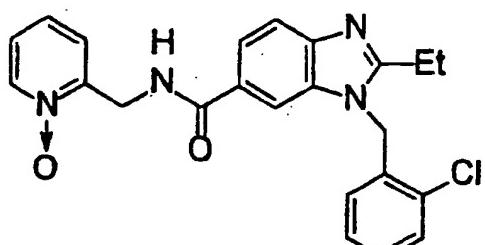


(82)

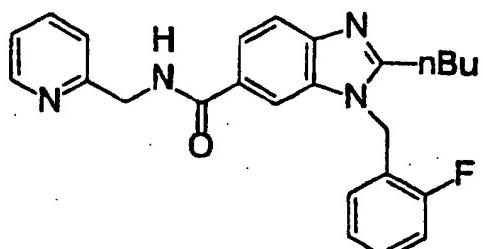


(83)

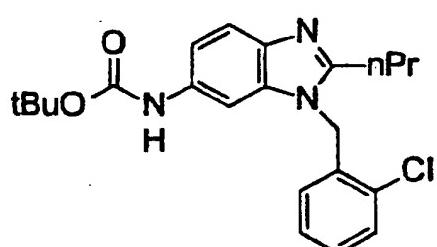
FIG. 8



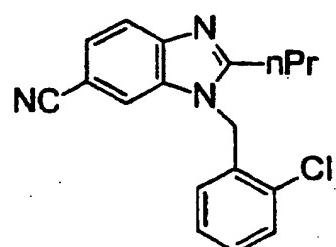
(84)



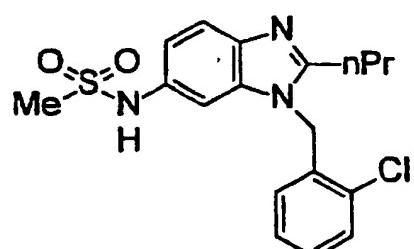
(85)



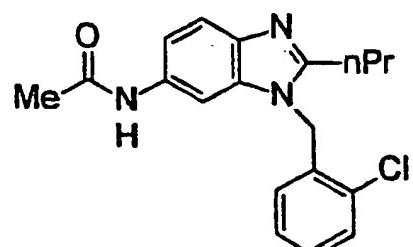
(86)



(87)

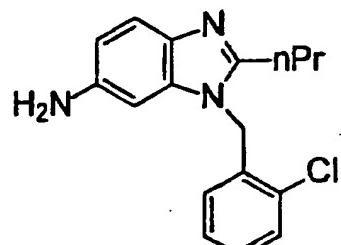


(88)

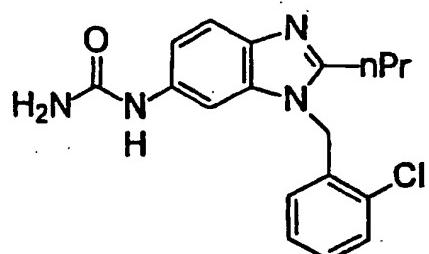


(89)

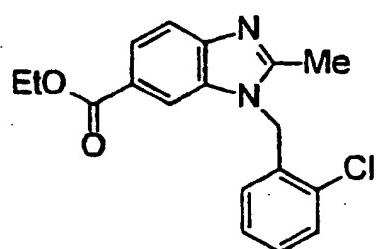
FIG. 9



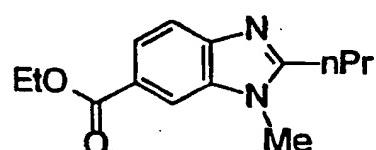
(90)



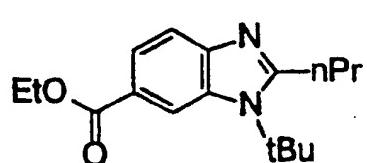
(91)



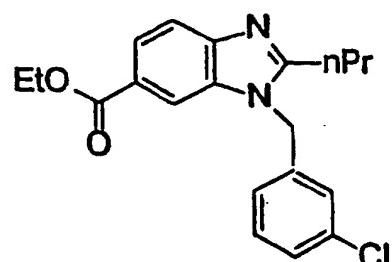
(92)



(93)

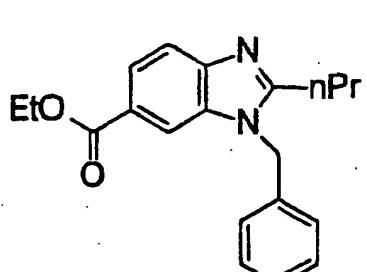


(94)

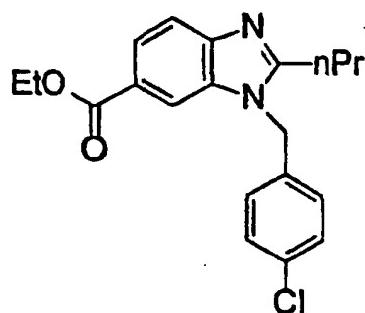


(95)

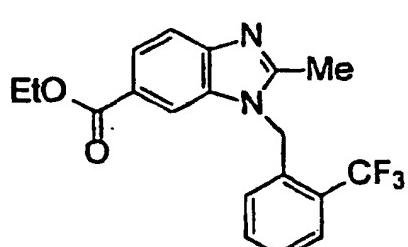
FIG. 10



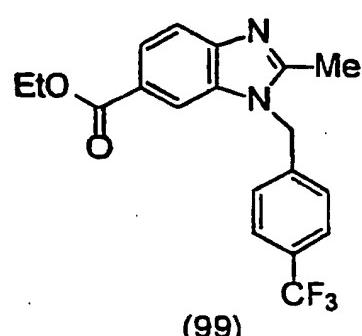
(96)



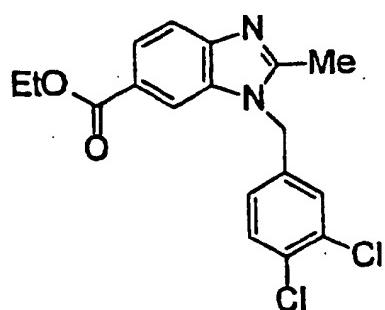
(97)



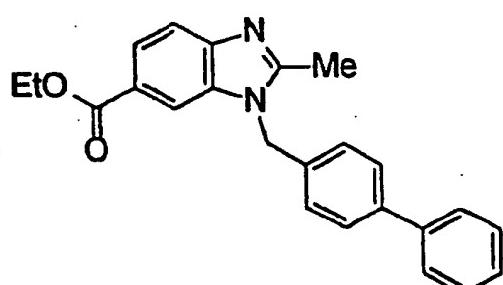
(98)



(99)

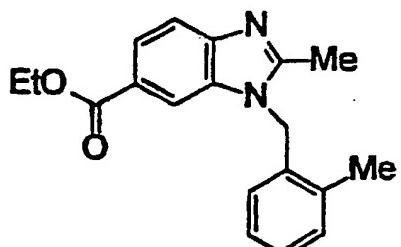


(100)

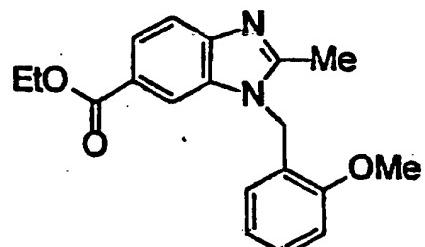


(101)

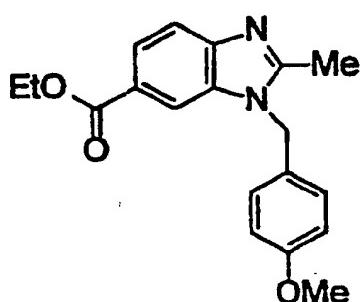
FIG. 11



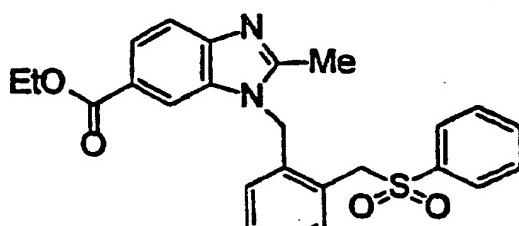
(102)



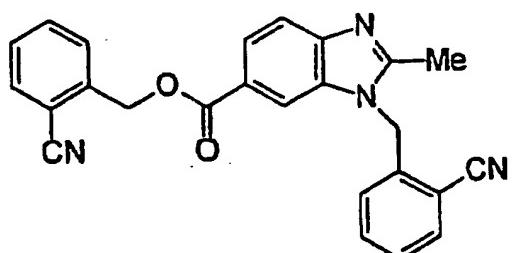
(103)



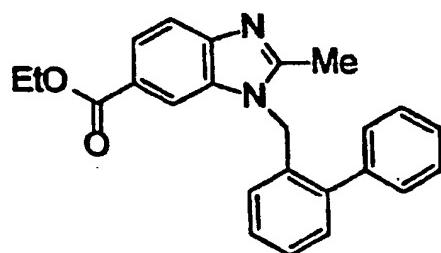
(104)



(105)

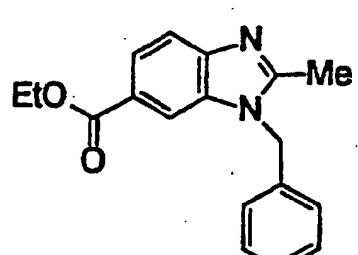


(106)

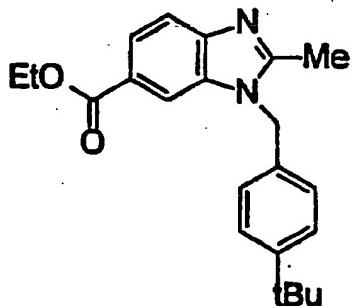


(107)

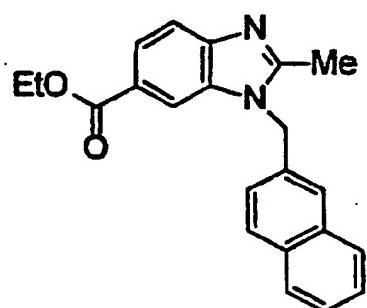
FIG. 12



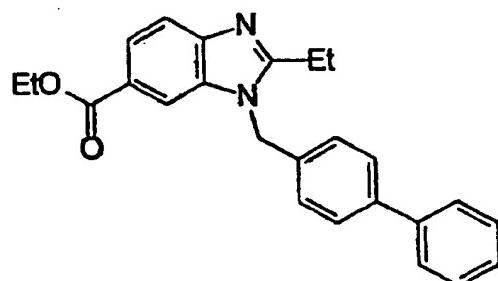
(108)



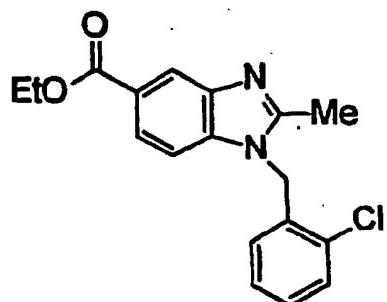
(109)



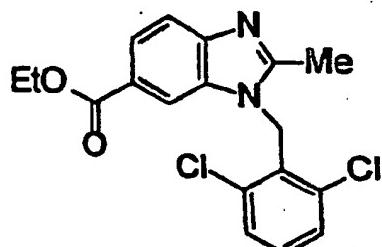
(110)



(111)

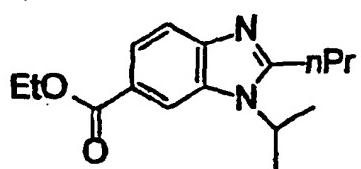


(112)

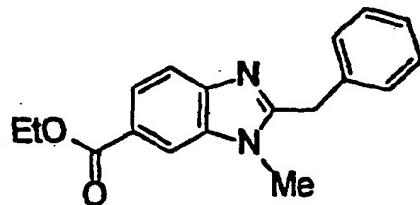


(113)

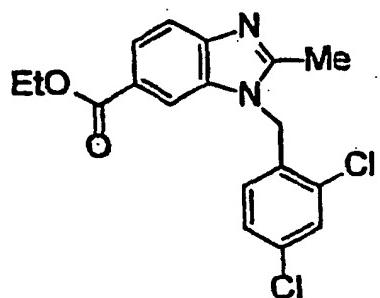
F I G . 1 3



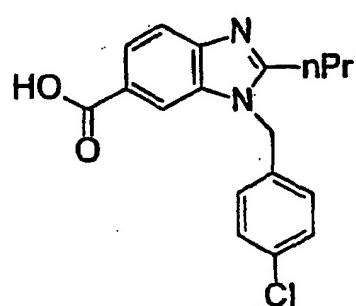
(114)



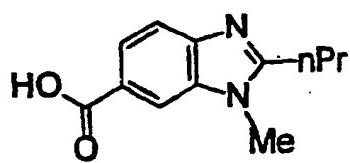
(115)



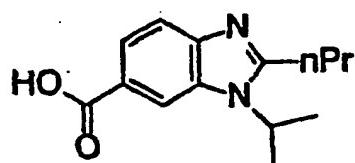
(116)



(117)

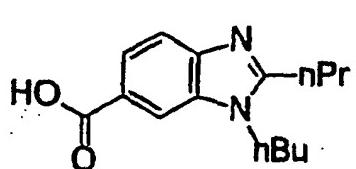


(118)

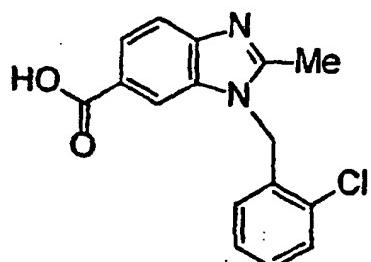


(119)

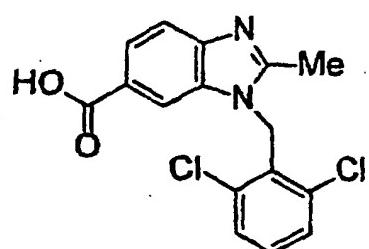
FIG. 14



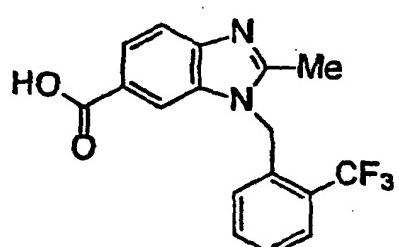
(120)



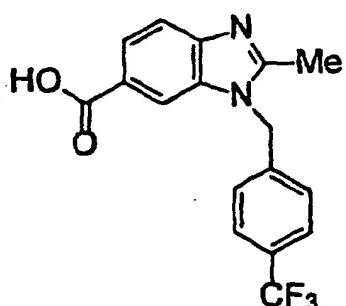
(121)



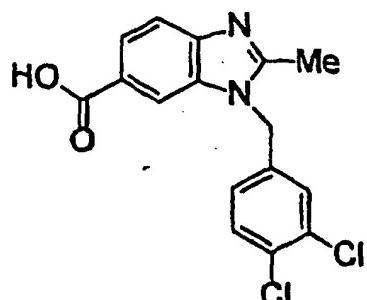
(122)



(123)

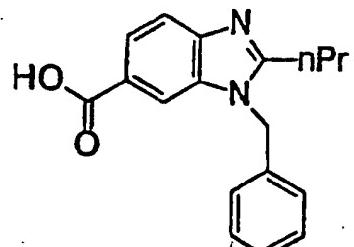


(124)

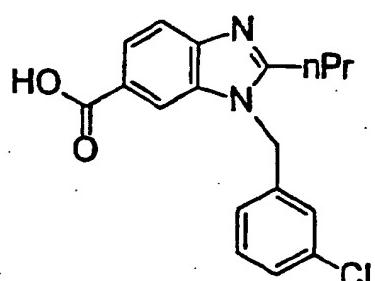


(125)

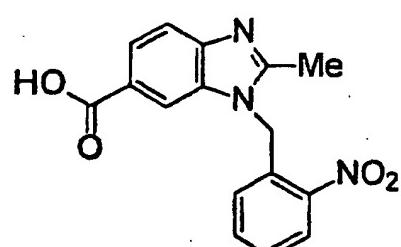
FIG. 15



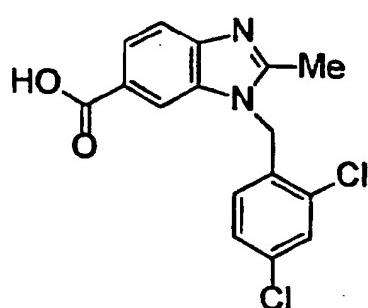
(126)



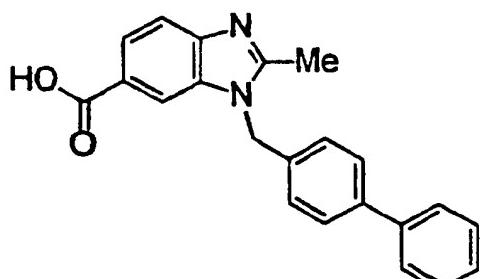
(127)



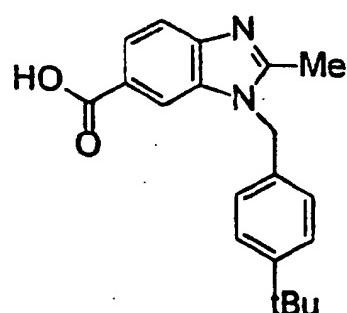
(128)



(129)

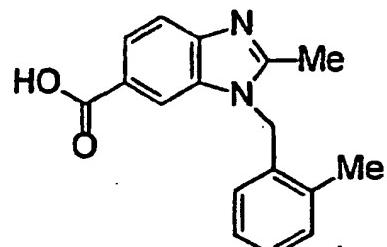


(130)

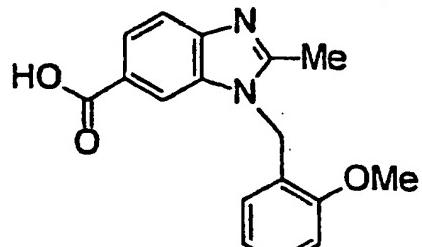


(131)

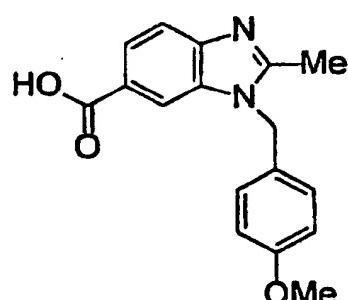
F I G . 1 6



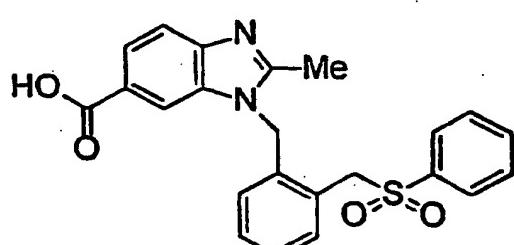
(132)



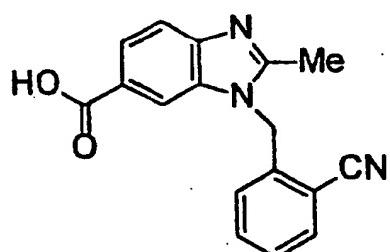
(133)



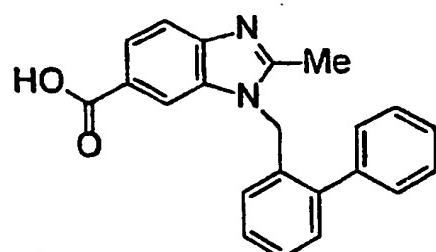
(134)



(135)

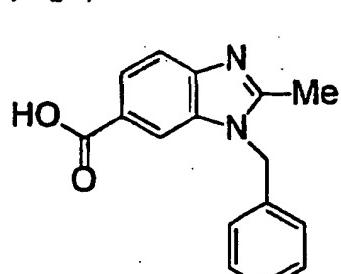


(136)

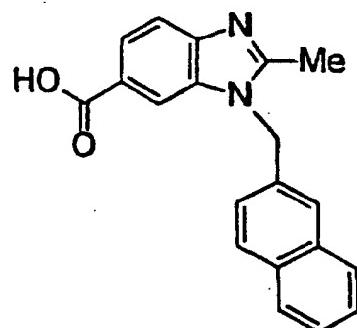


(137)

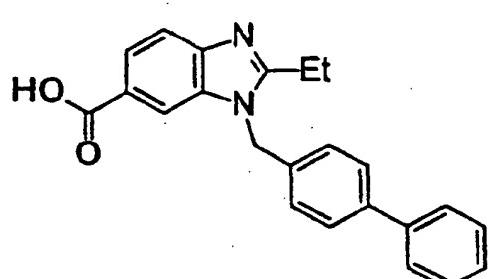
F I G . 1 7



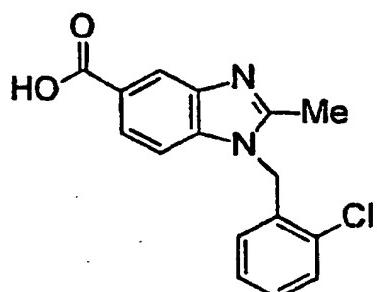
(138)



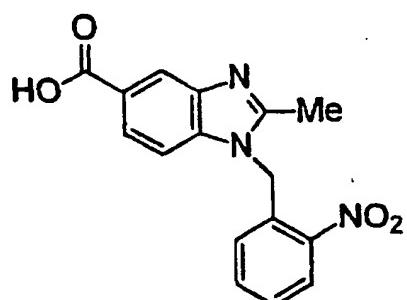
(139)



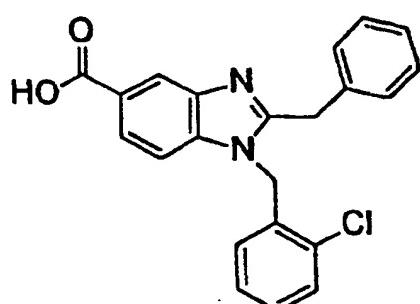
(140)



(141)

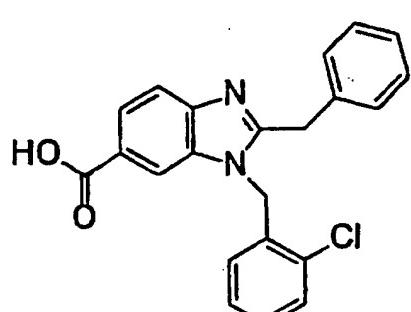


(142)

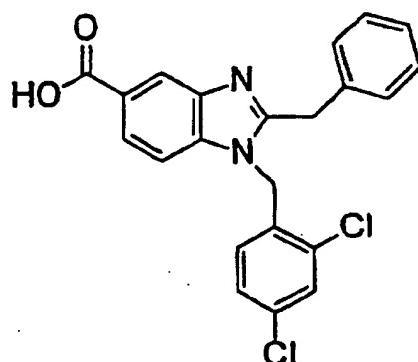


(143)

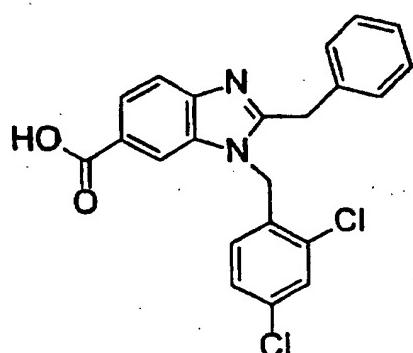
FIG. 18



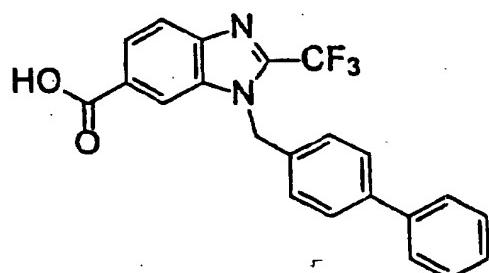
(144)



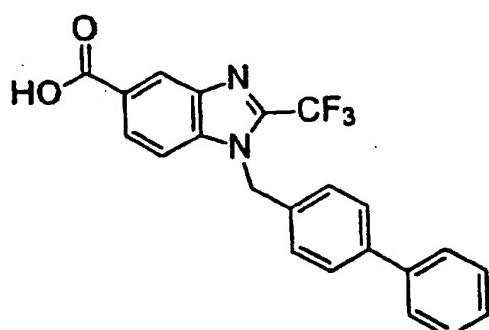
(145)



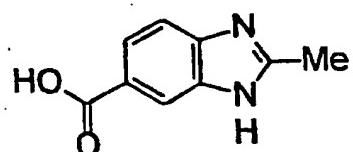
(146)



(147)

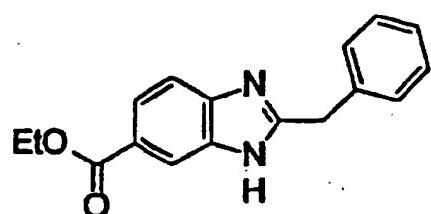


(148)

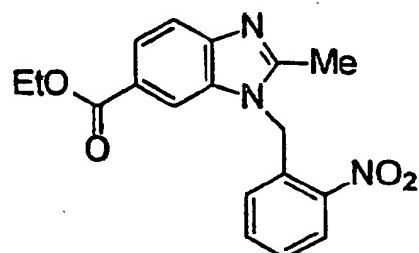


(149)

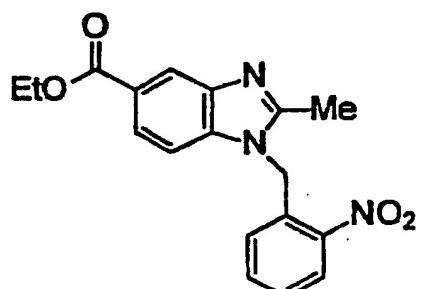
FIG. 19



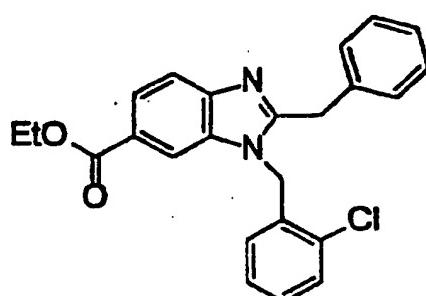
(150)



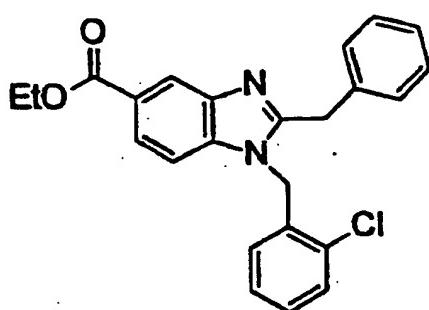
(151)



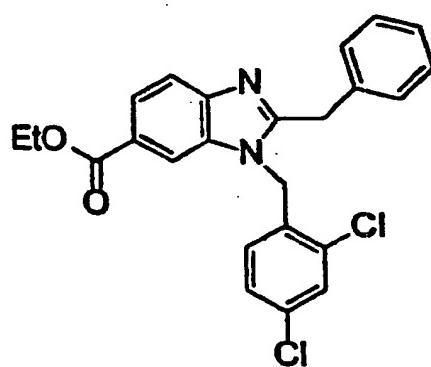
(152)



(153)

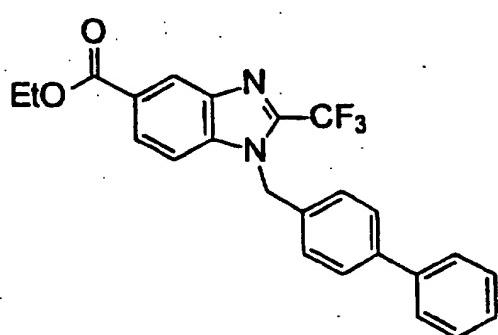
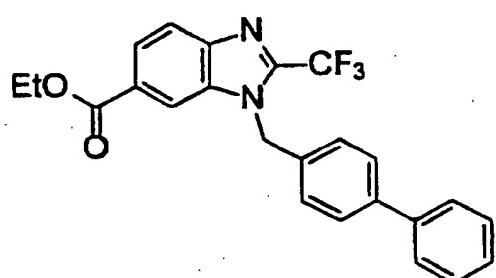
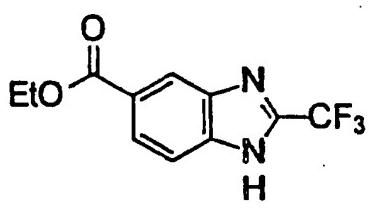
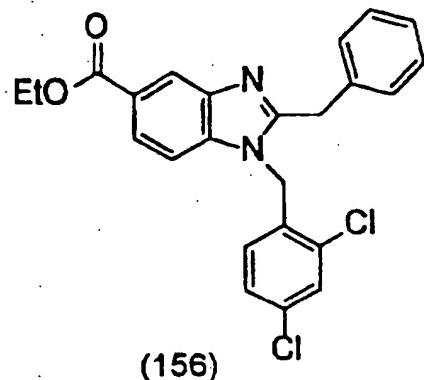


(154)



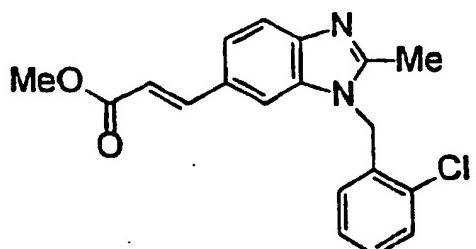
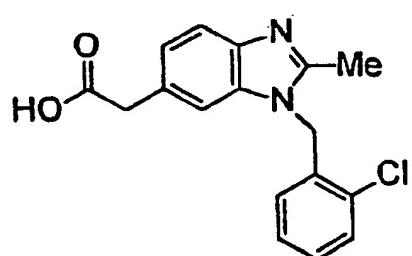
(155)

FIG. 20



(158)

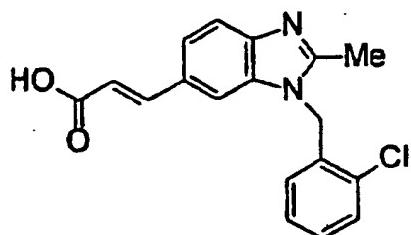
(159)



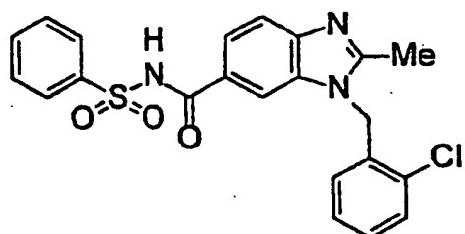
(160)

(161)

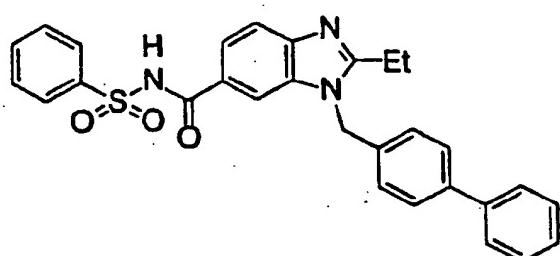
FIG. 21



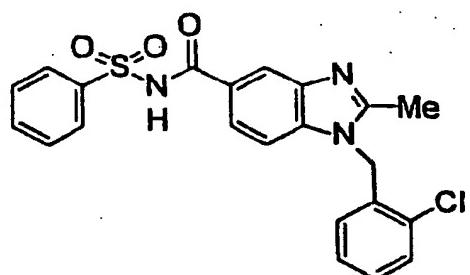
(162)



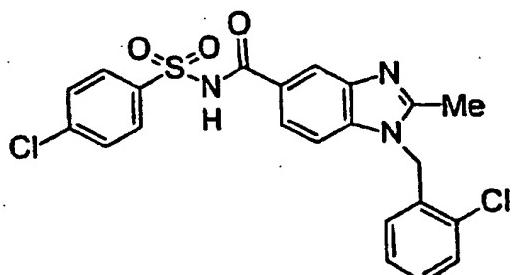
(163)



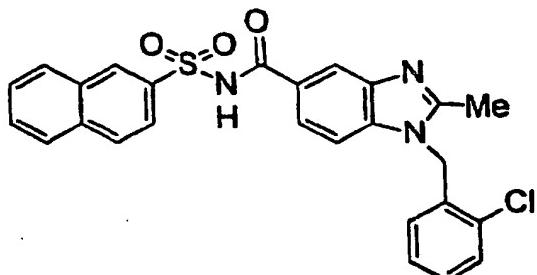
(164)



(165)

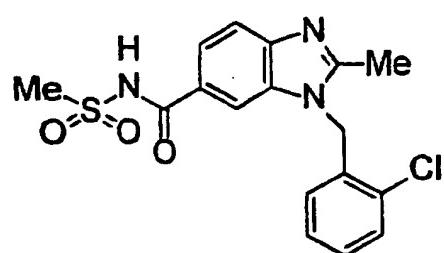


(166)

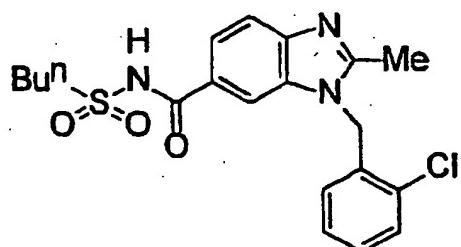


(167)

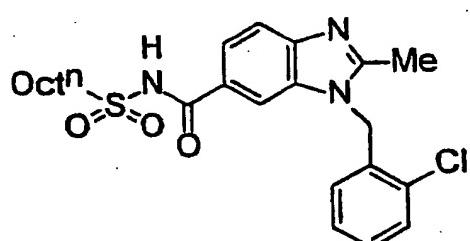
FIG. 22



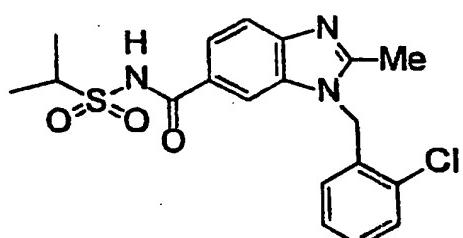
(168)



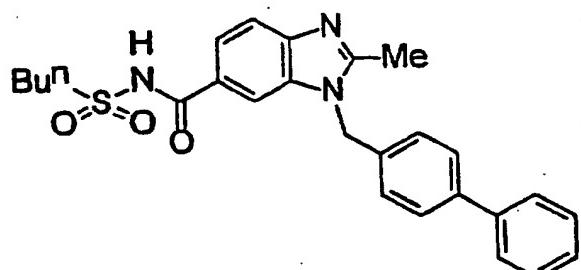
(169)



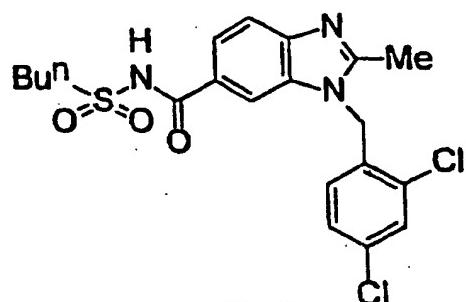
(170)



(171)

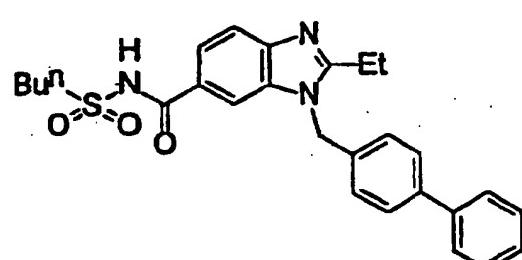


(172)

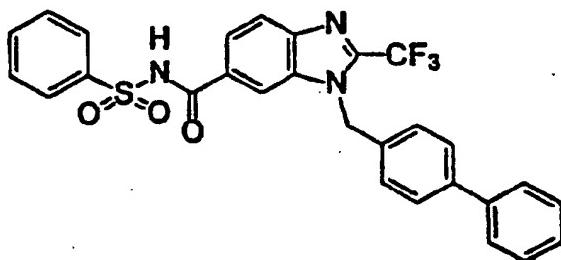


(173)

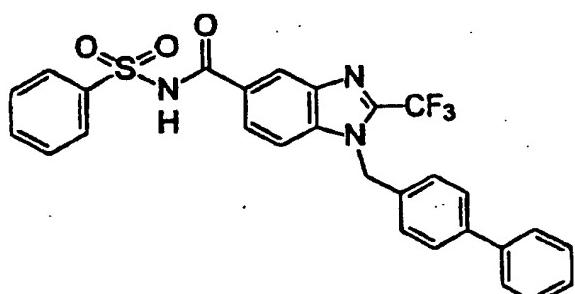
FIG. 23



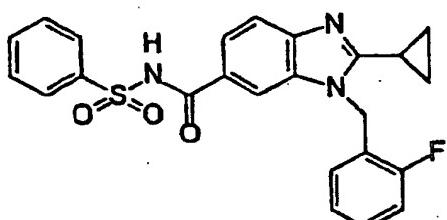
(174)



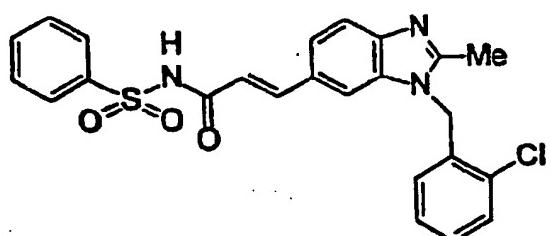
(175)



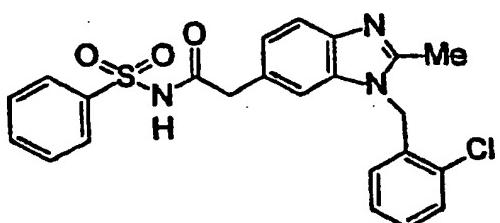
(176)



(177)

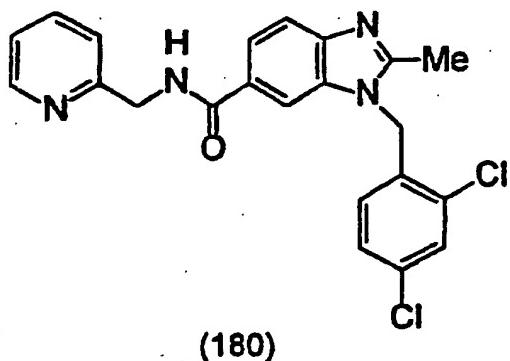


(178)

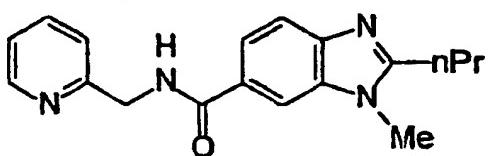


(179)

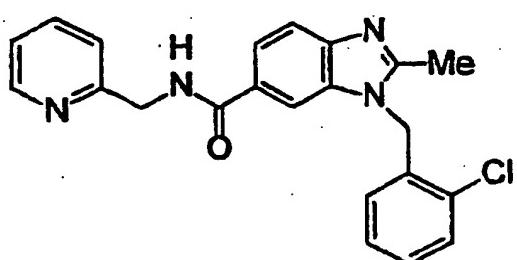
FIG. 24



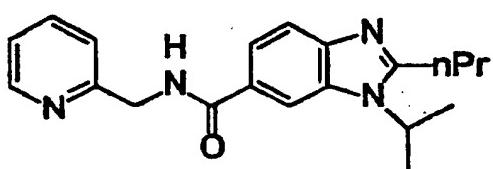
(180)



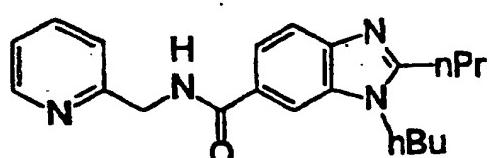
(181)



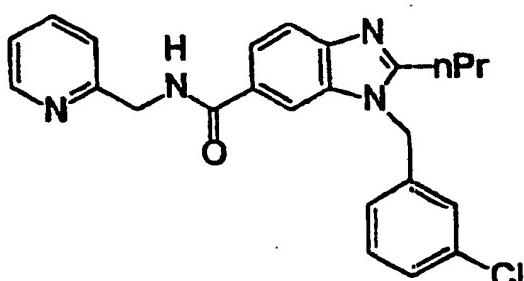
(182)



(183)

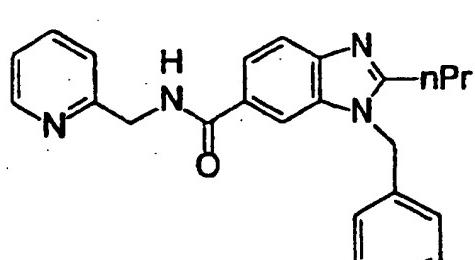


(184)

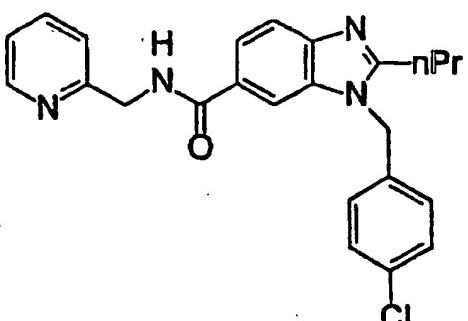


(185)

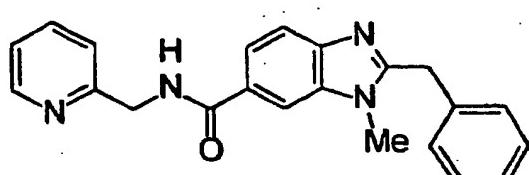
FIG. 25



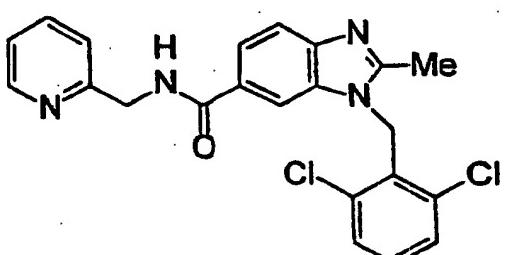
(186)



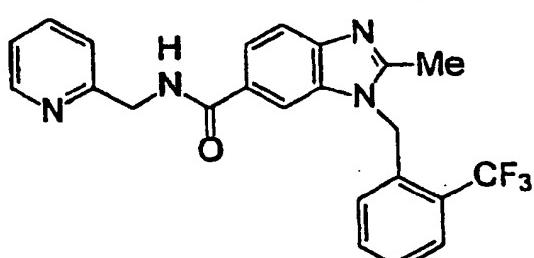
(187)



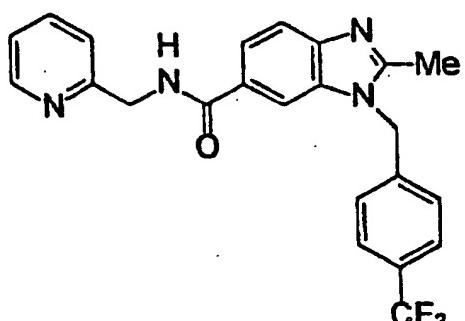
(188)



(189)

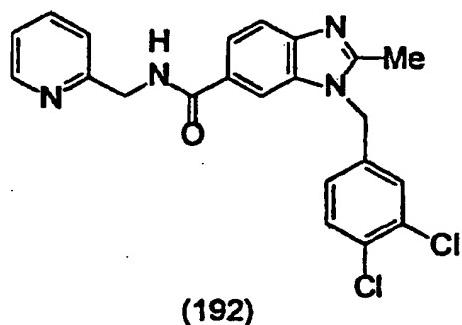


(190)

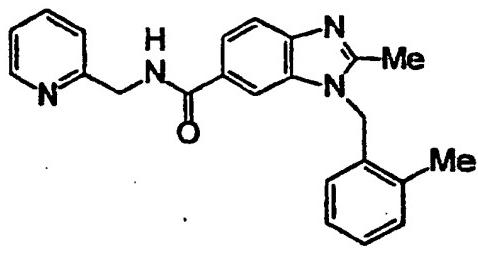


(191)

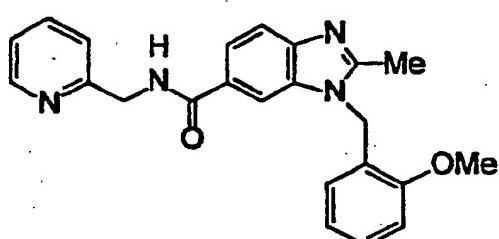
FIG. 26



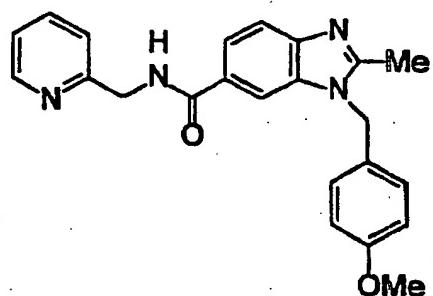
(192)



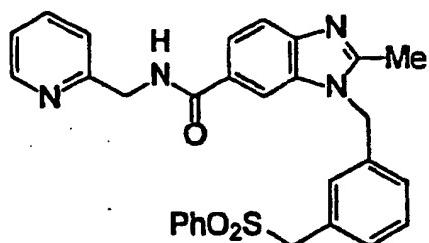
(193)



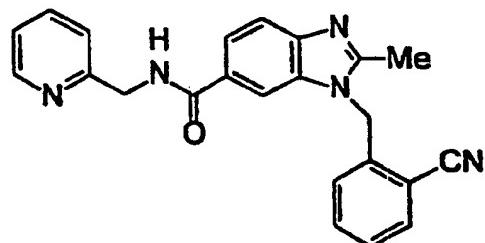
(194)



(195)

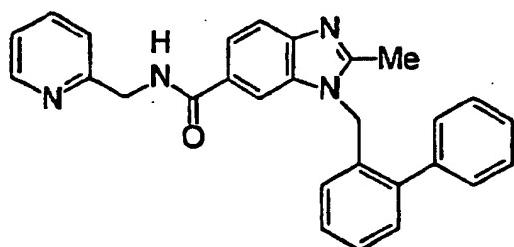


(196)

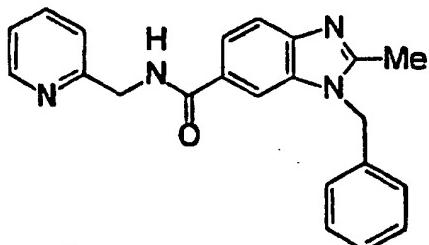


(197)

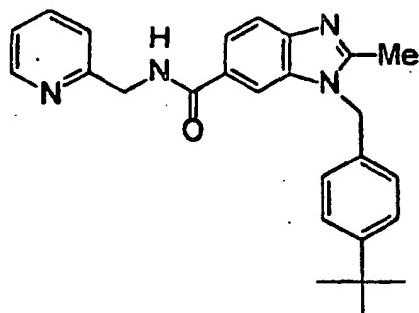
FIG. 27



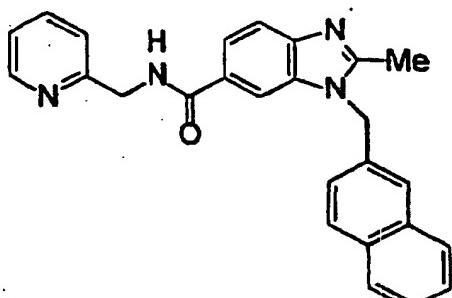
(198)



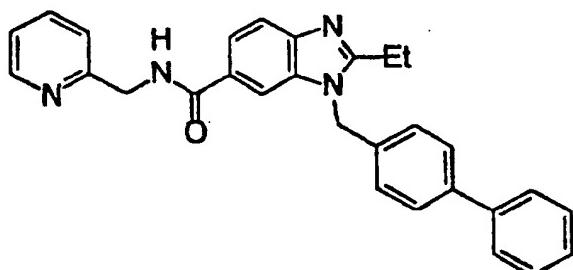
(199)



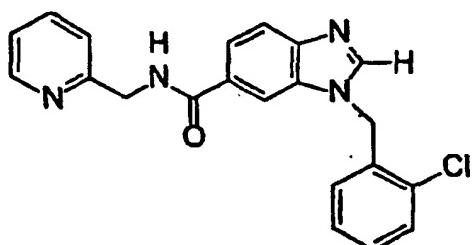
(200)



(201)

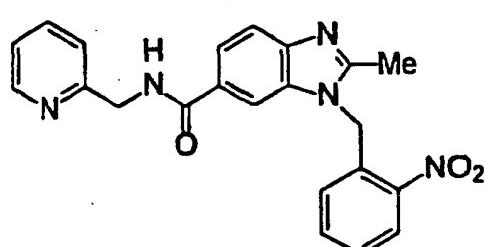


(202)

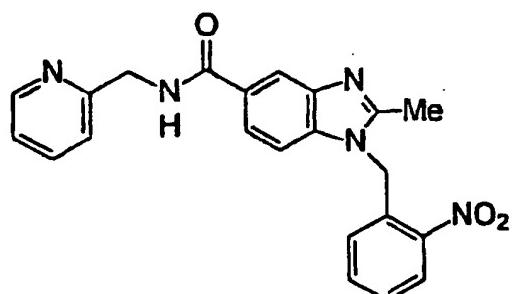


(203)

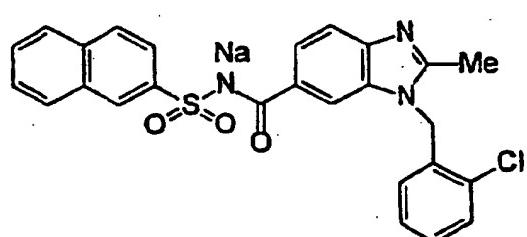
FIG. 28



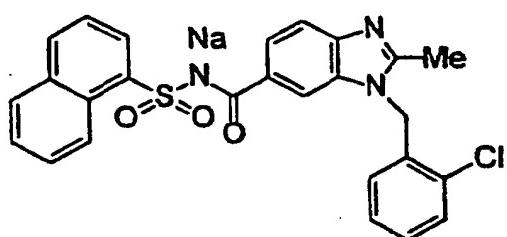
(204)



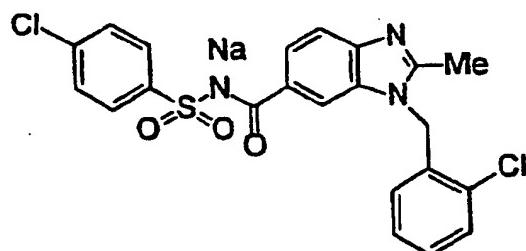
(205)



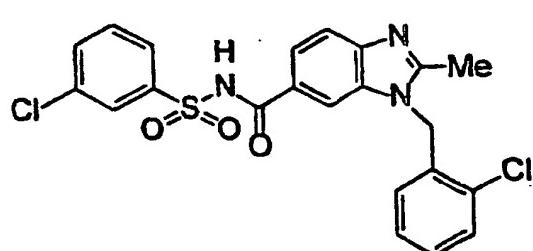
(206)



(207)

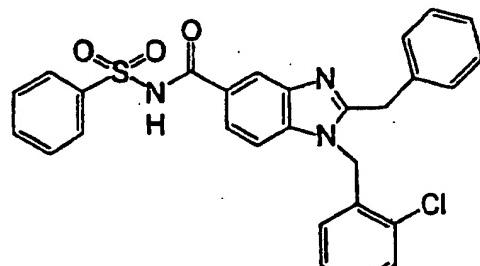


(208)

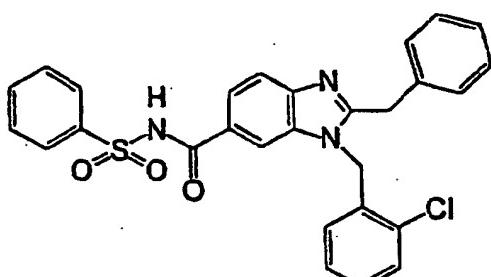


(209)

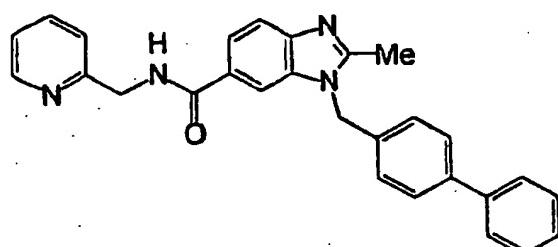
FIG. 29



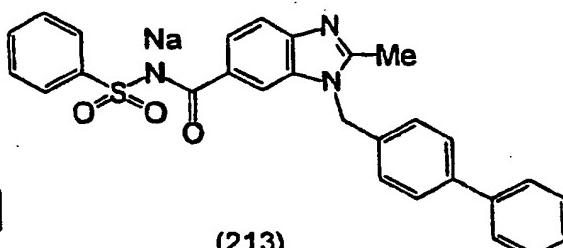
(210)



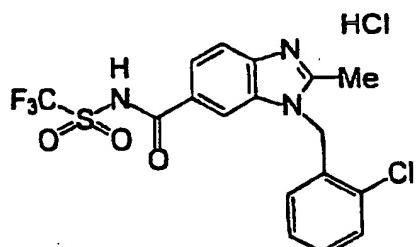
(211)



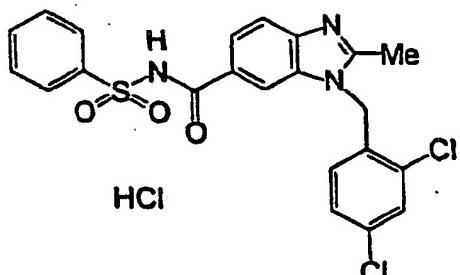
(212)



(213)

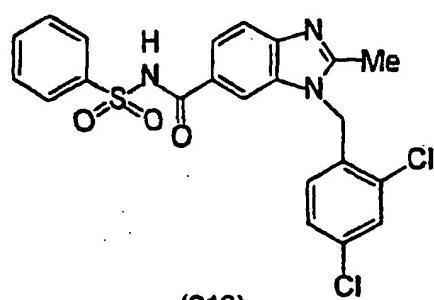


(214)

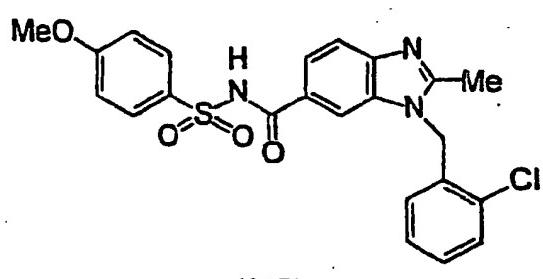


(215)

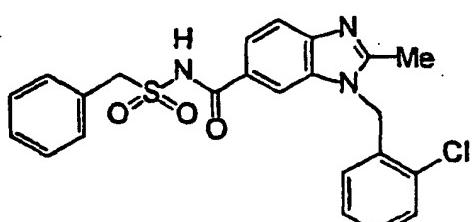
FIG. 30.



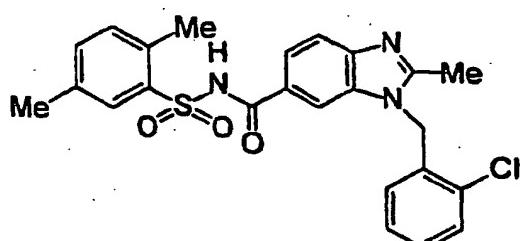
(216)



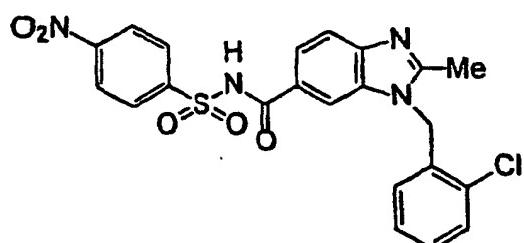
(217)



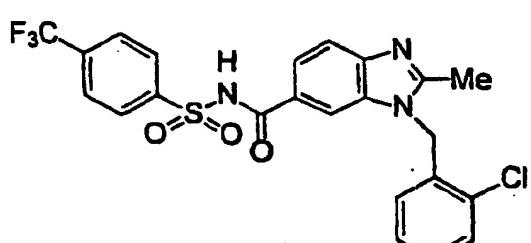
(218)



(219)

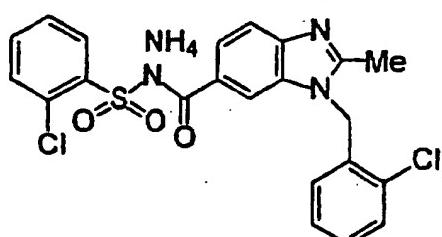


(220)

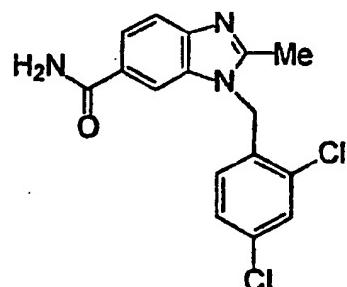


(221)

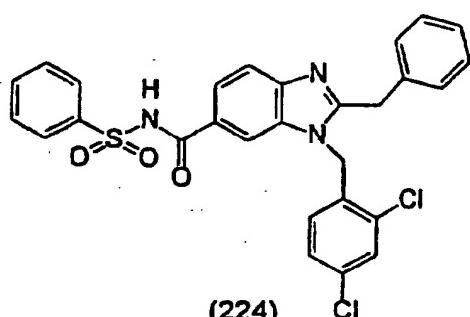
FIG. 31



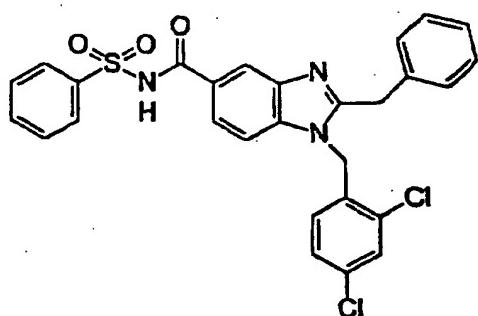
(222)



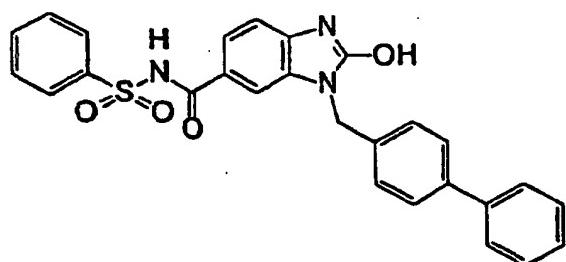
(223)



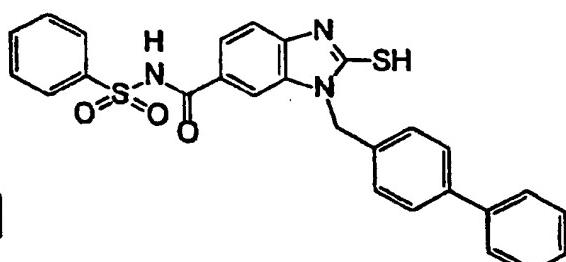
(224)



(225)



(226)



(227)

FIG. 32

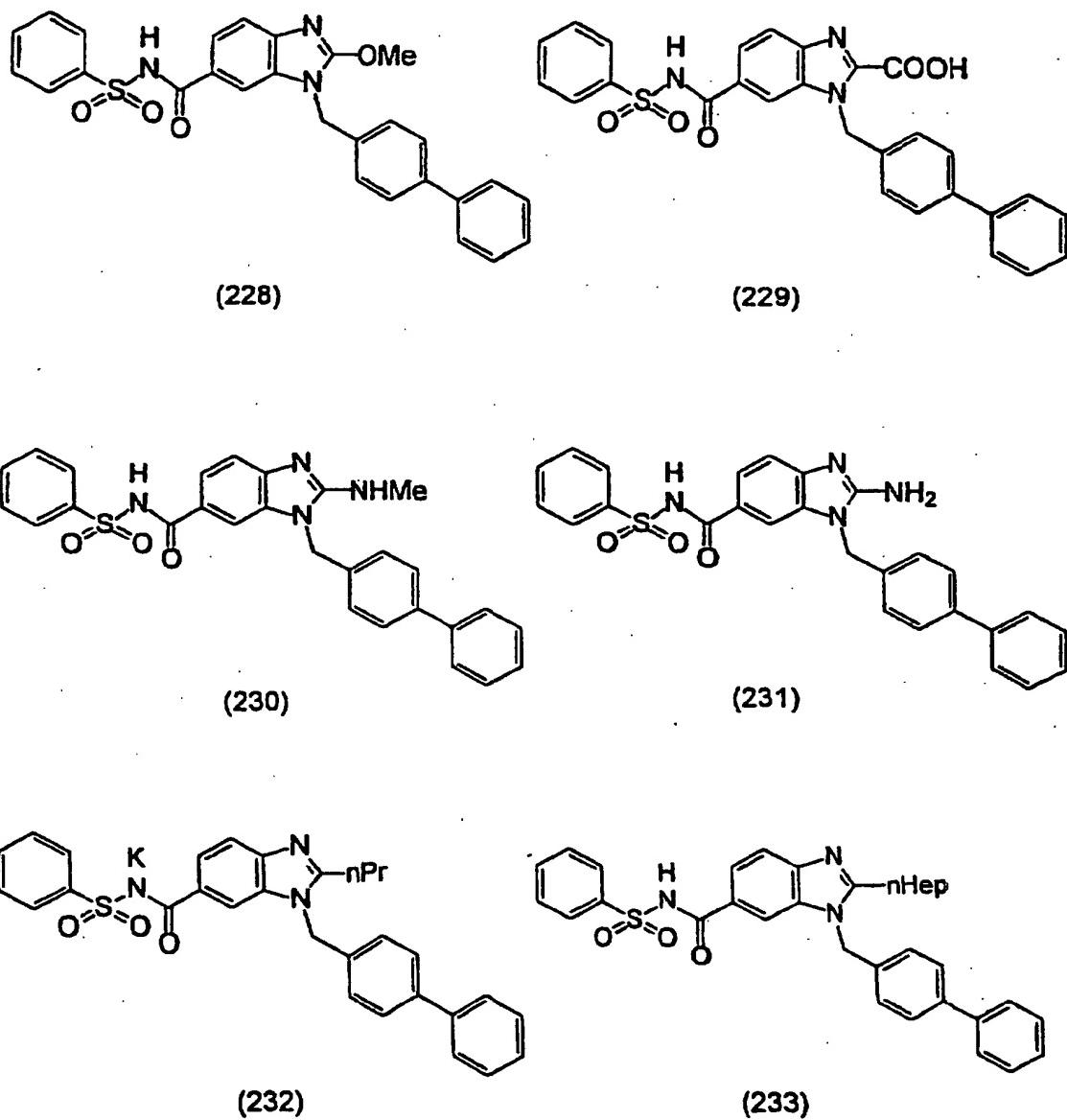
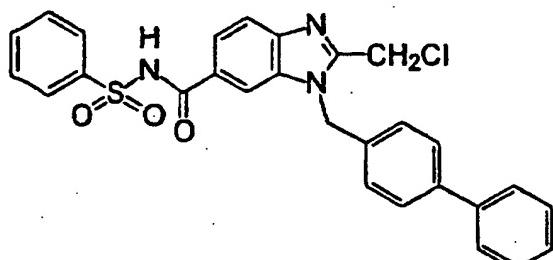
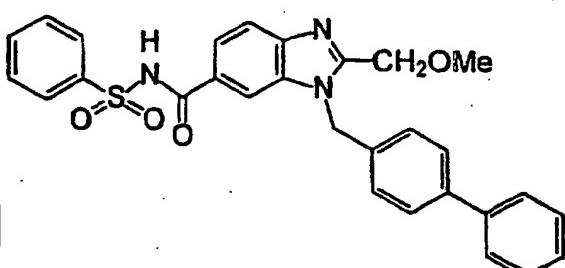


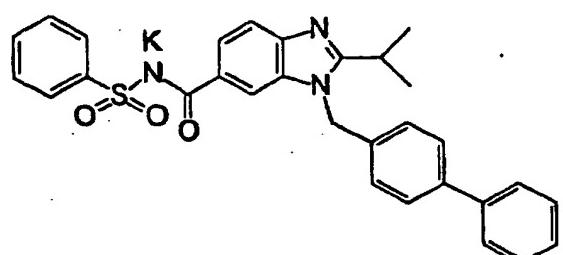
FIG. 33



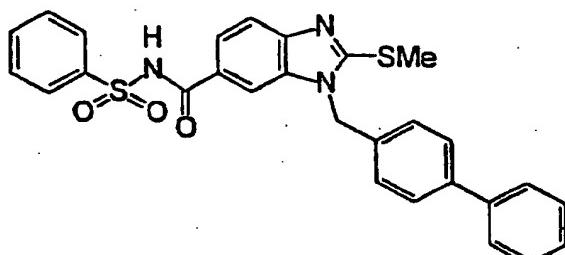
(234)



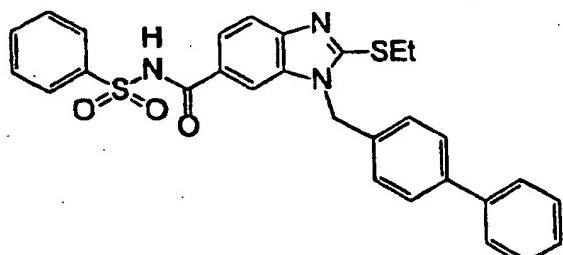
(235)



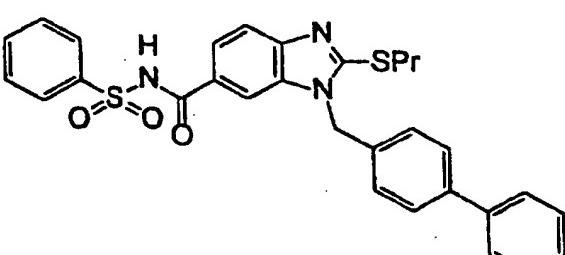
(236)



(237)

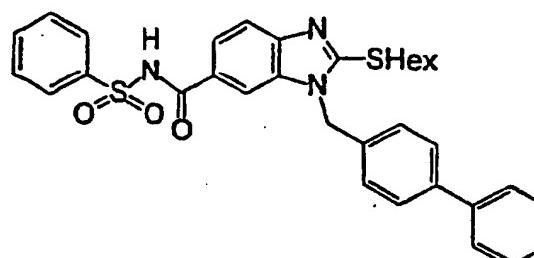


(238)

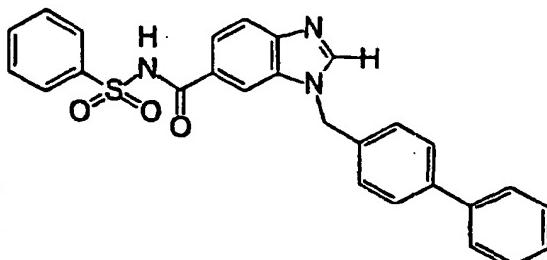


(239)

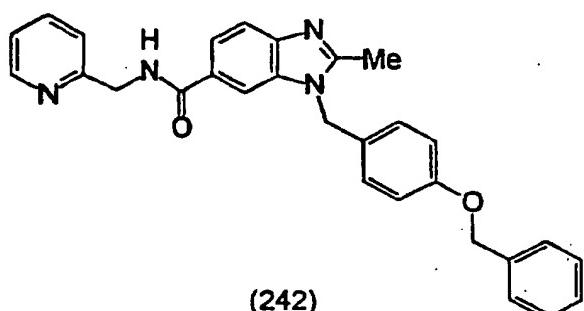
FIG. 34



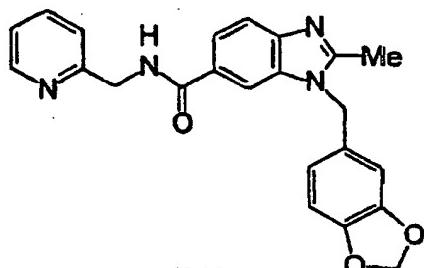
(240)



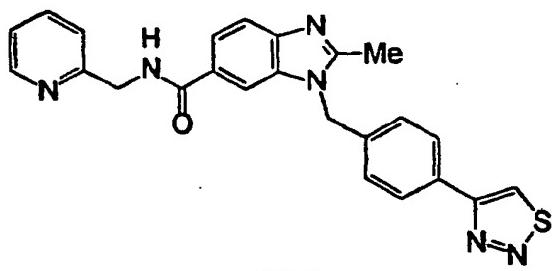
(241)



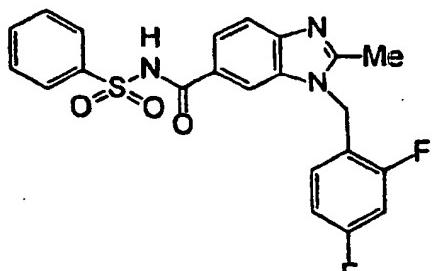
(242)



(243)

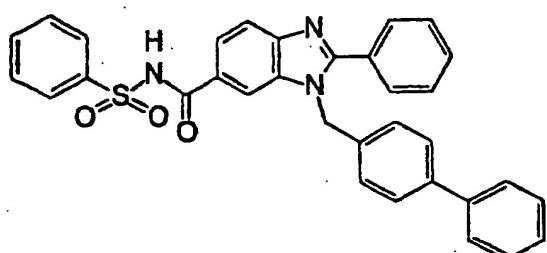


(244)

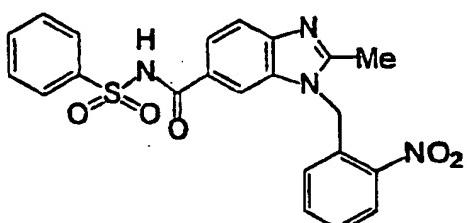


(245)

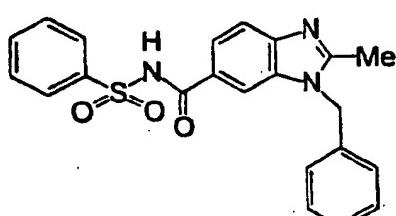
FIG. 35



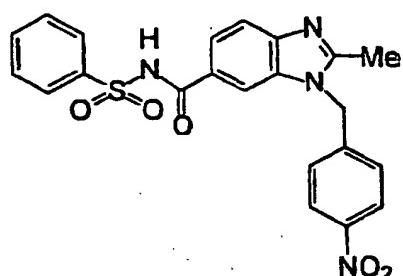
(246)



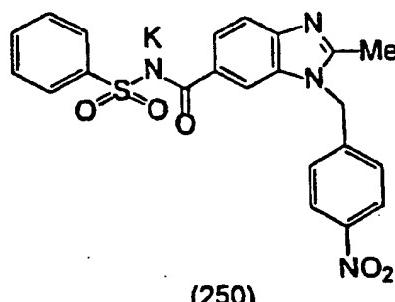
(247)



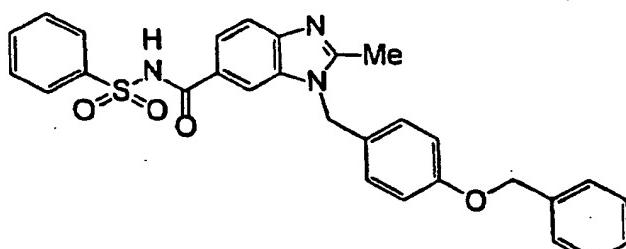
(248)



(249)

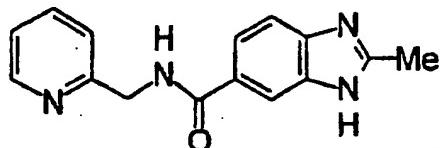


(250)

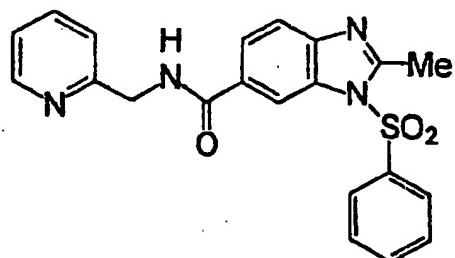


(251)

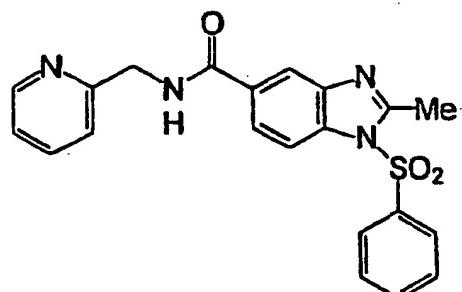
FIG. 36



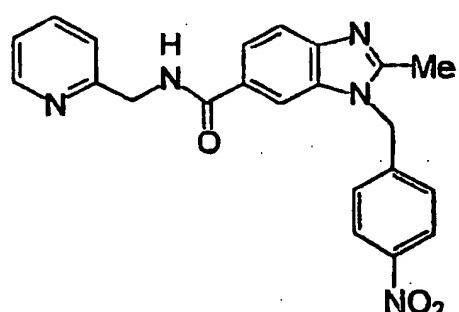
(252)



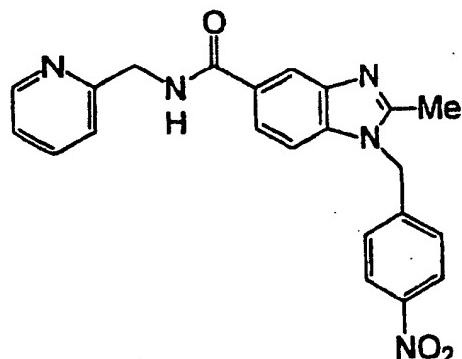
(253)



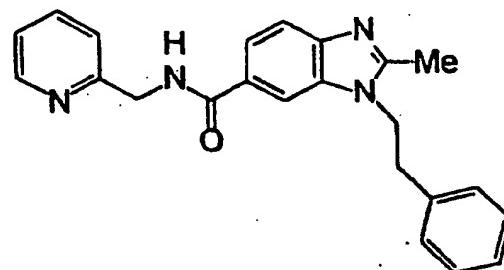
(254)



(255)



(256)



(257)

FIG. 37

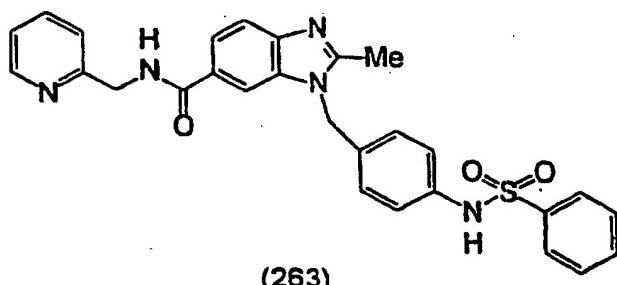
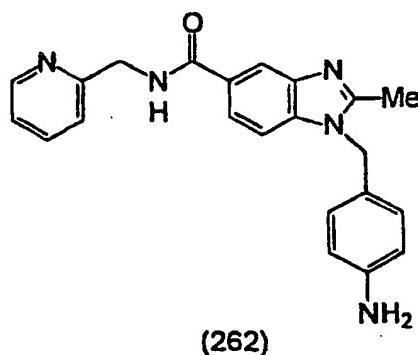
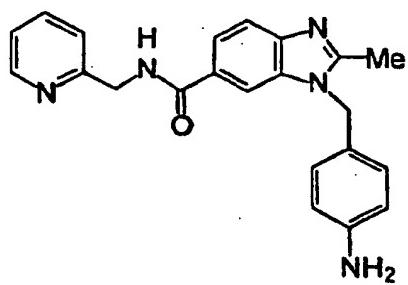
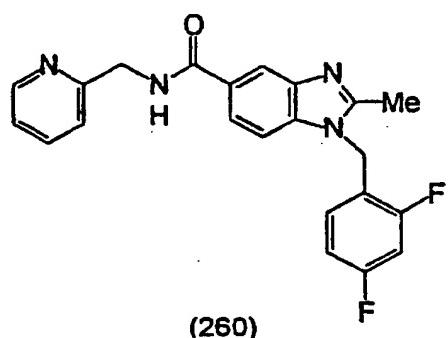
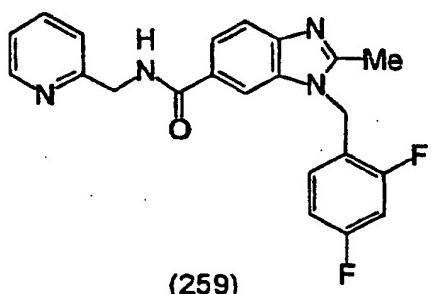
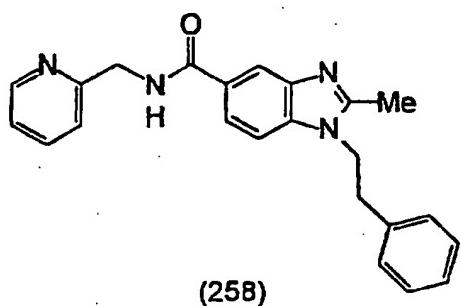
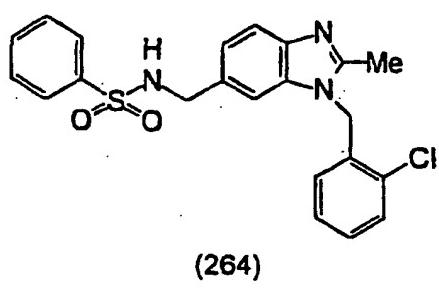
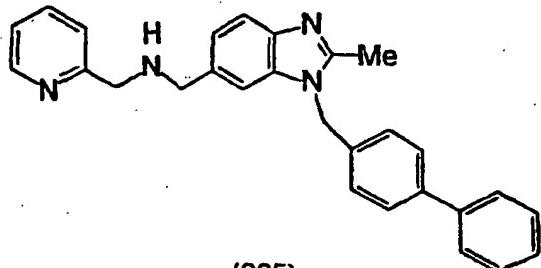


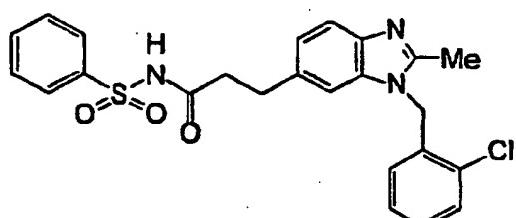
FIG. 38



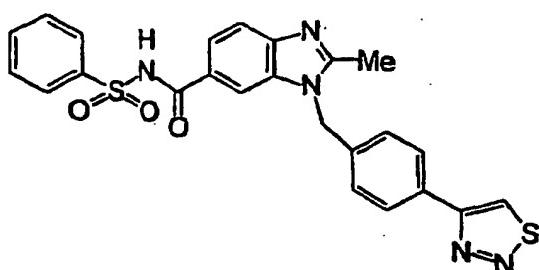
(264)



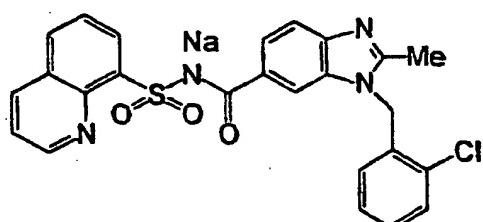
(265)



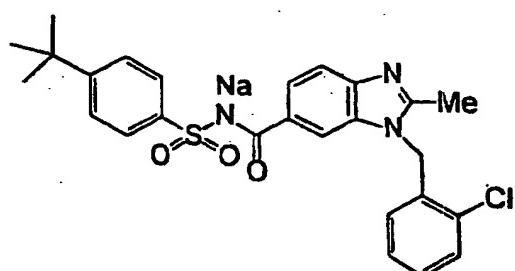
(266)



(267)



(268)



(269)

FIG. 39

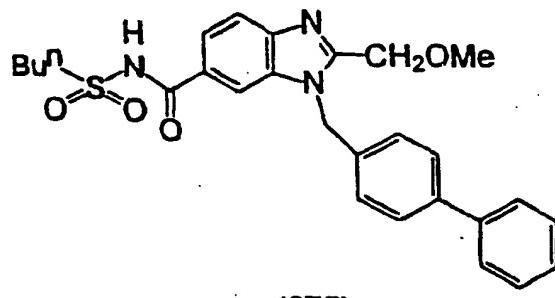
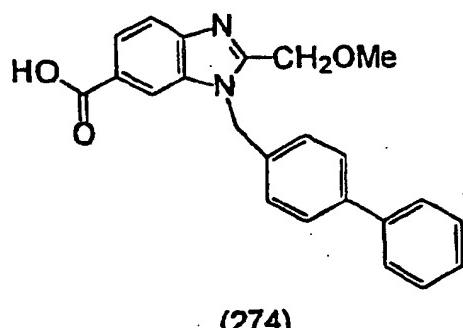
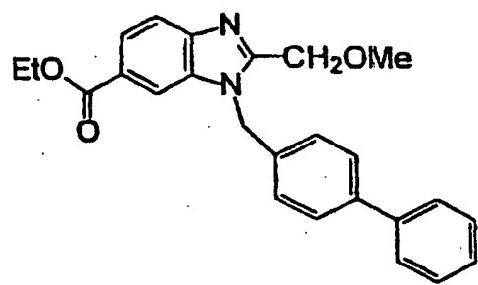
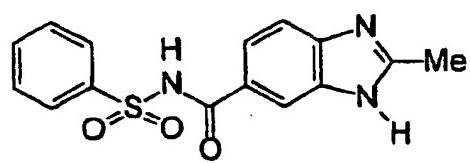
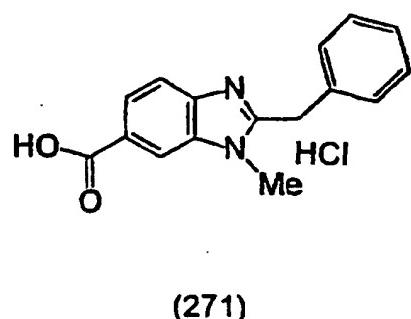
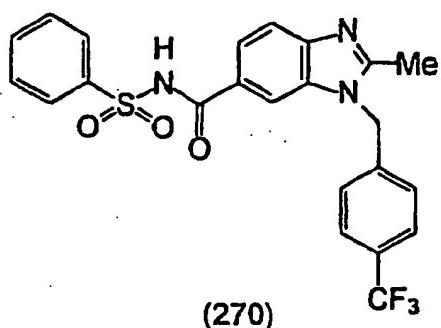


FIG. 40

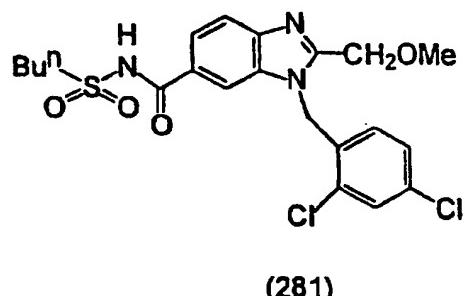
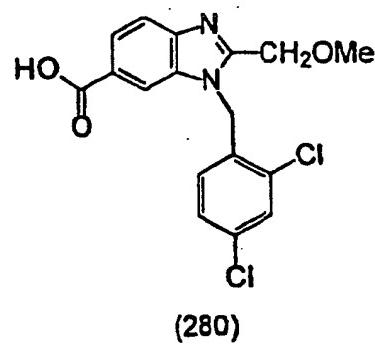
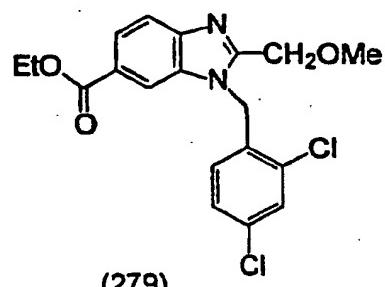
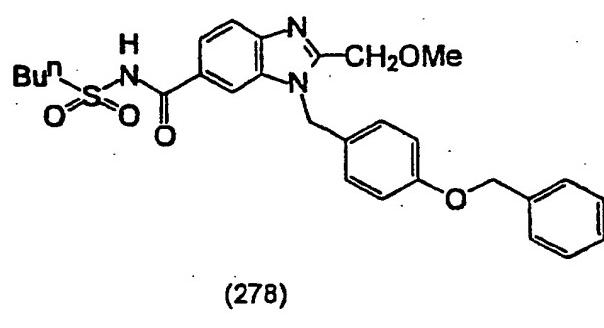
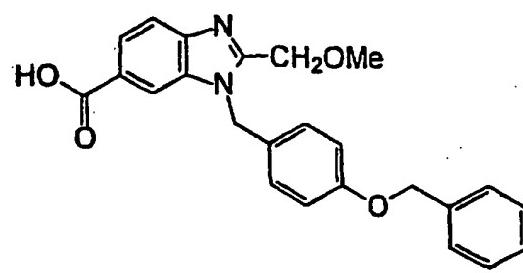
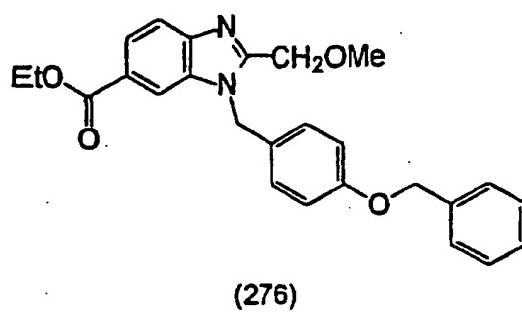
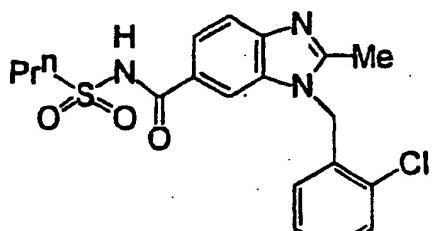
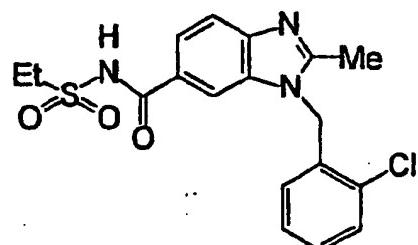


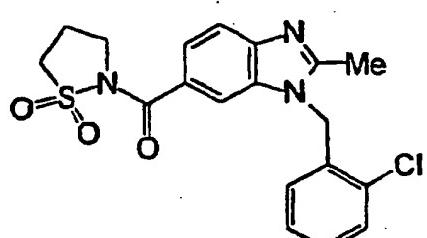
FIG. 41



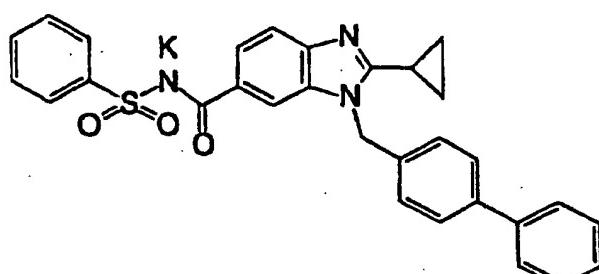
(282)



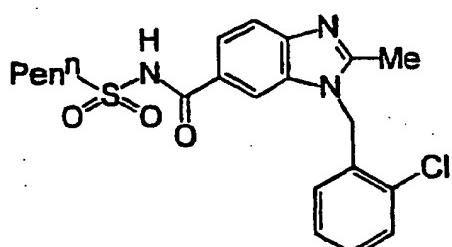
(283)



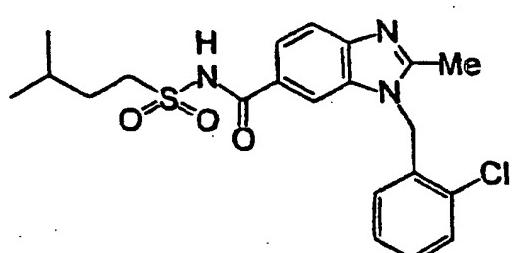
(284)



(285)

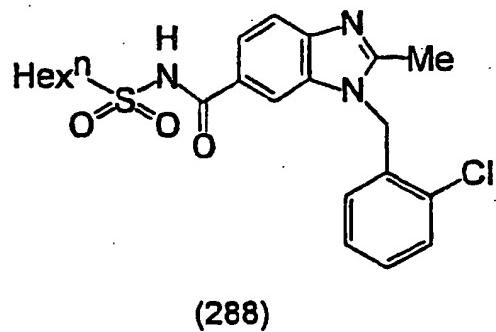


(286)

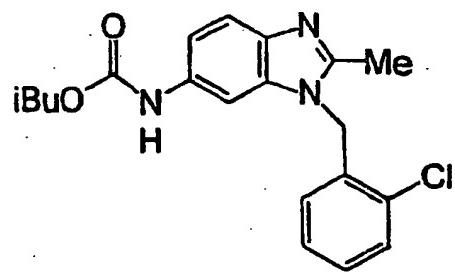


(287)

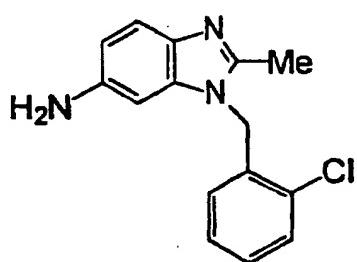
FIG. 42



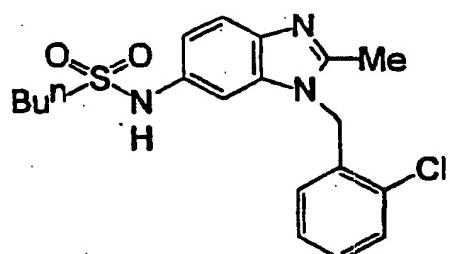
(288)



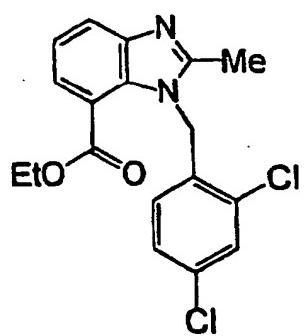
(289)



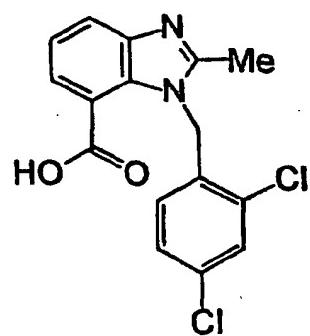
(290)



(291)

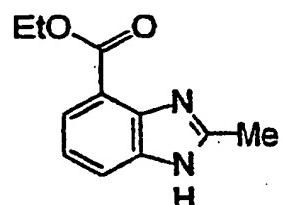
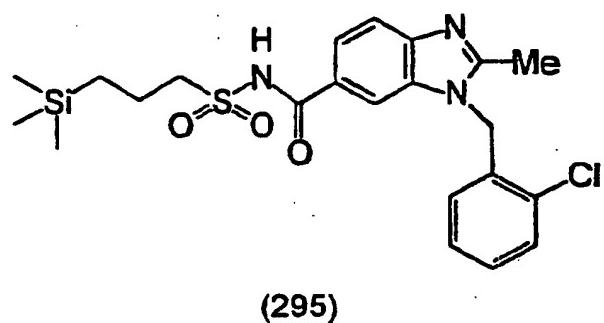
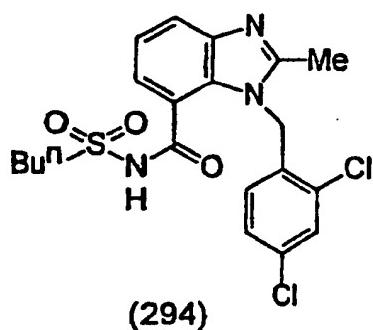


(292)

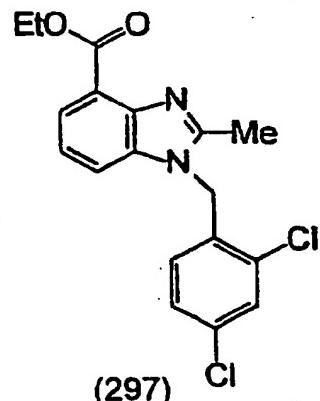


(293)

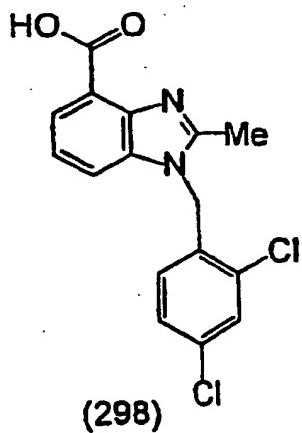
FIG. 43



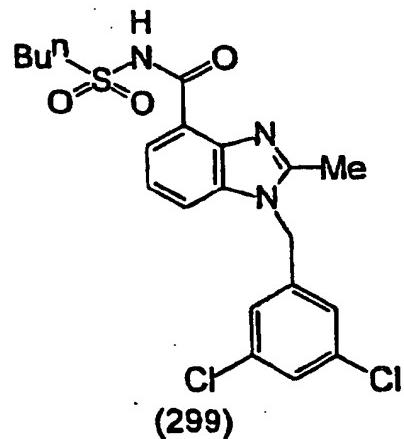
(296)



(297)



(298)



(299)

FIG. 44

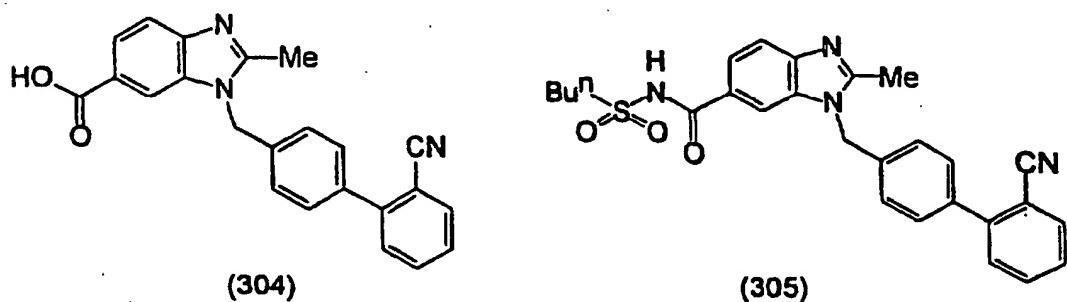
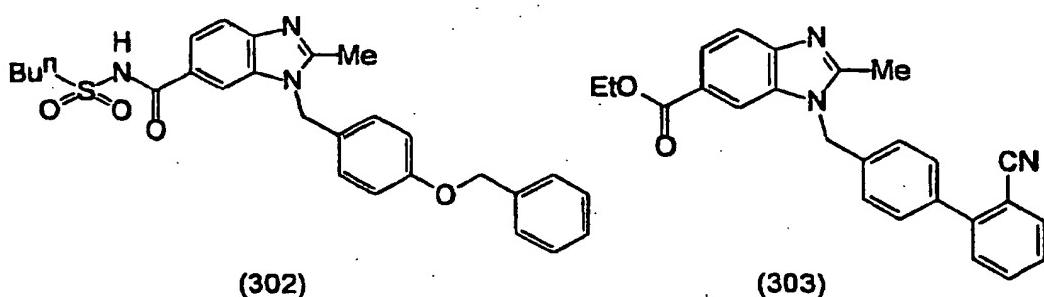
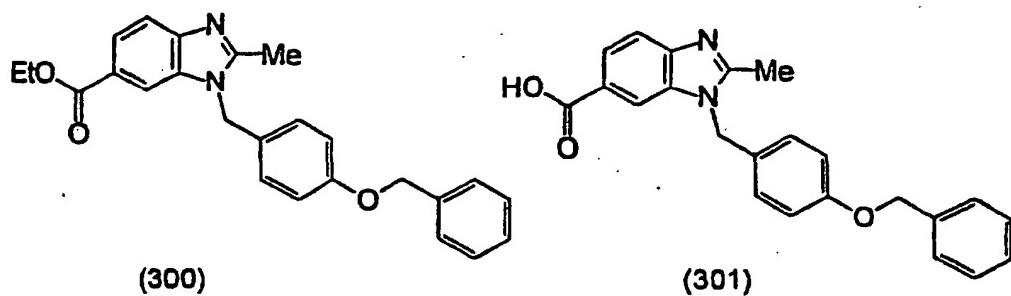
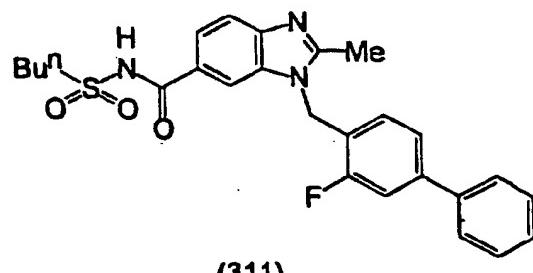
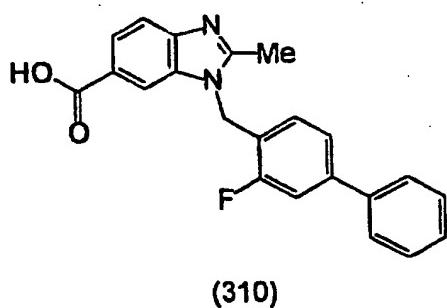
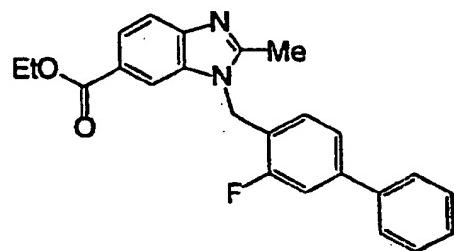
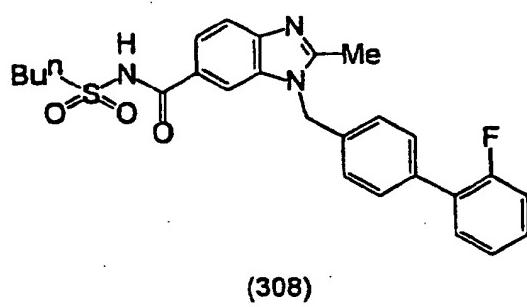
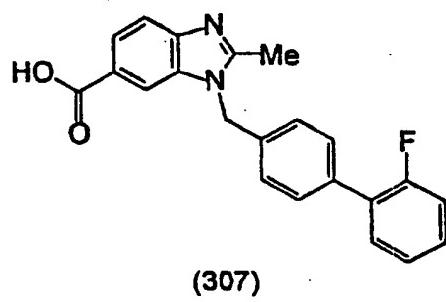
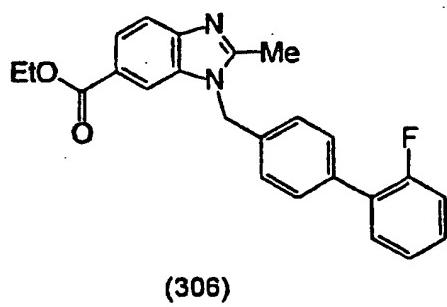


FIG. 45



F I G . 4 6

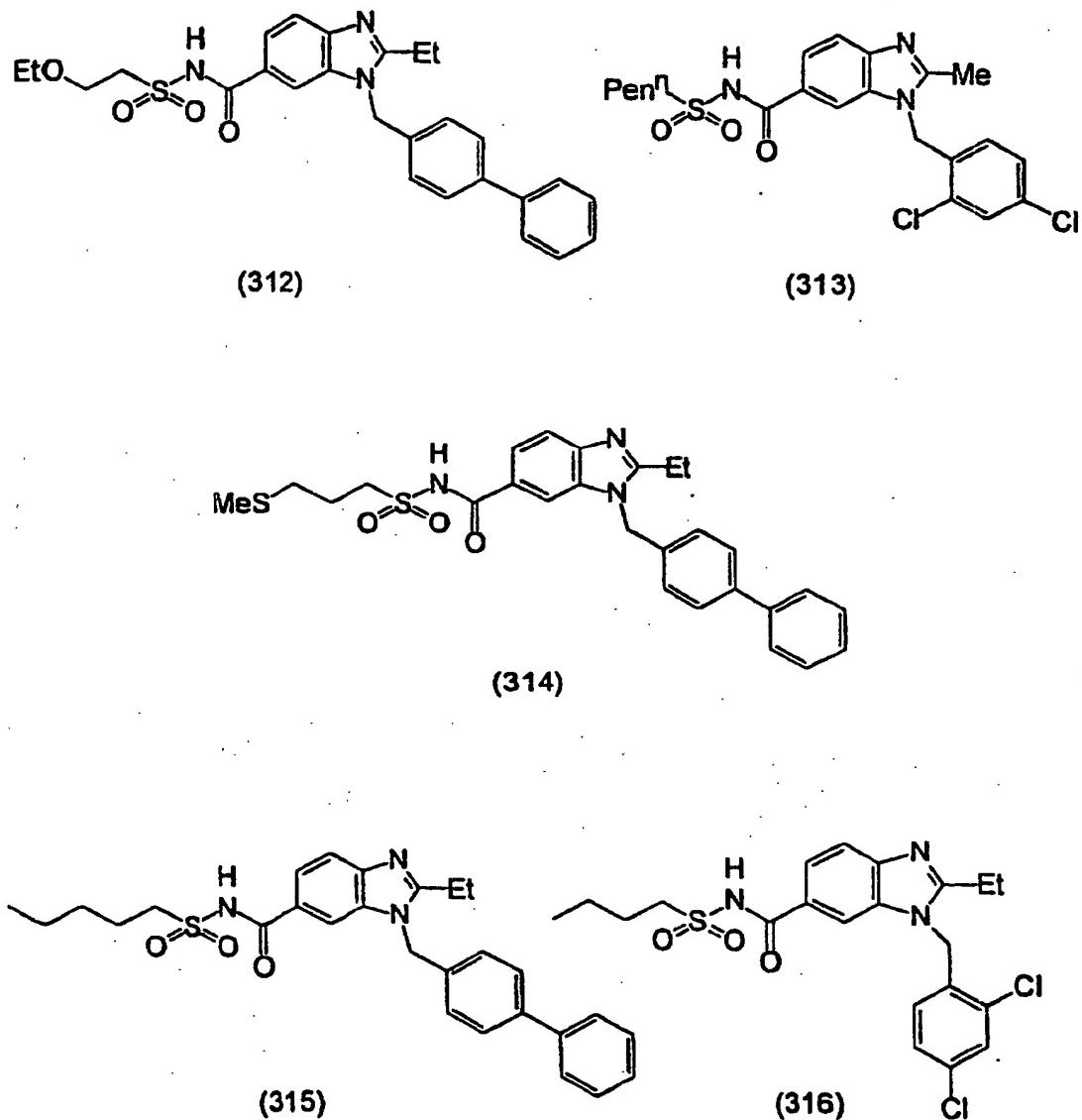


FIG. 47

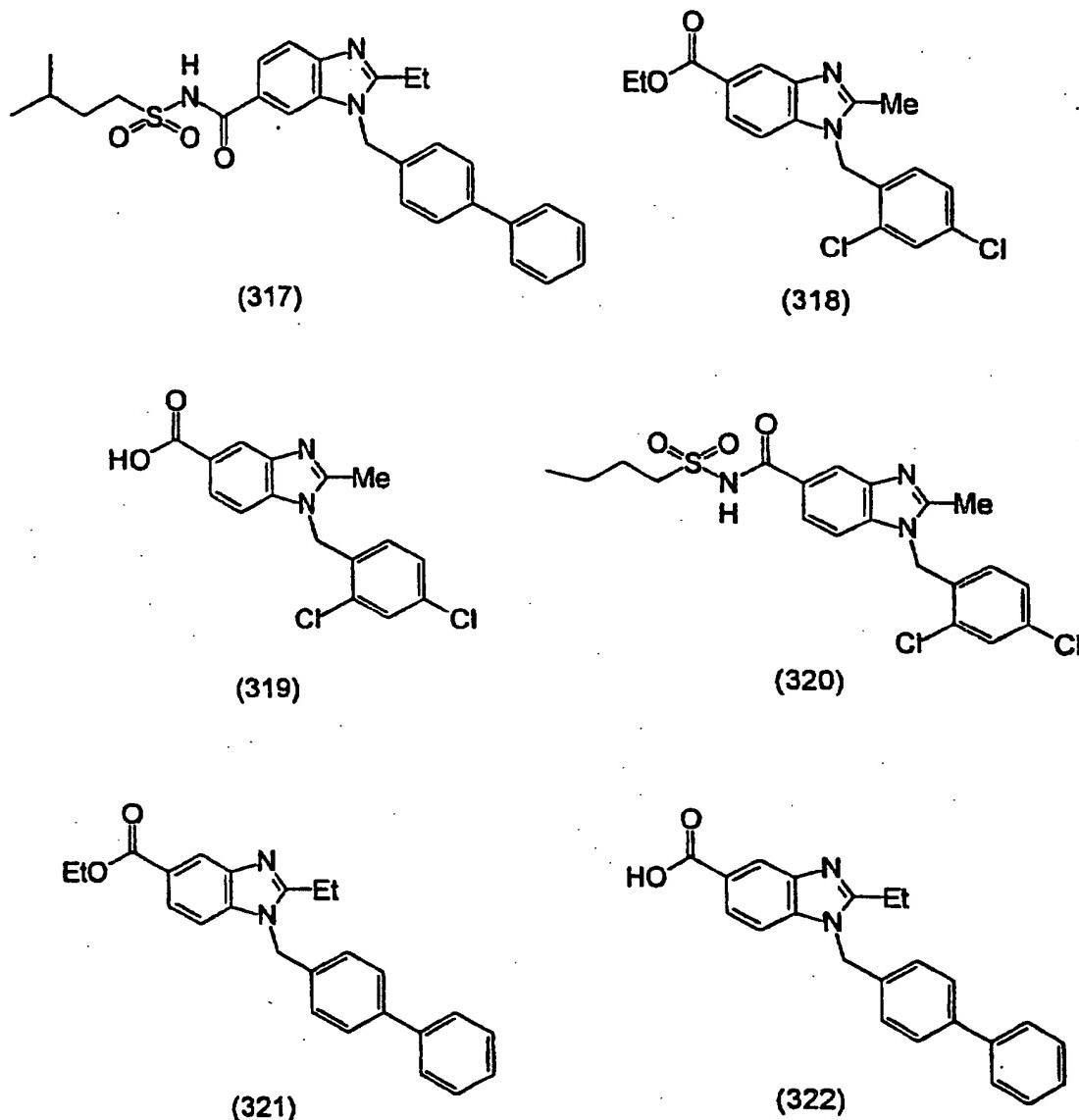


FIG. 48

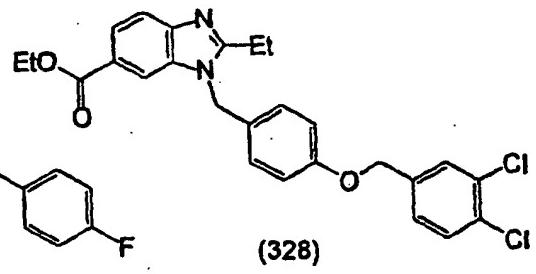
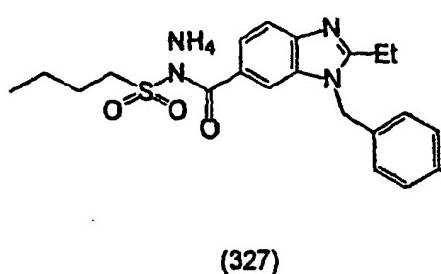
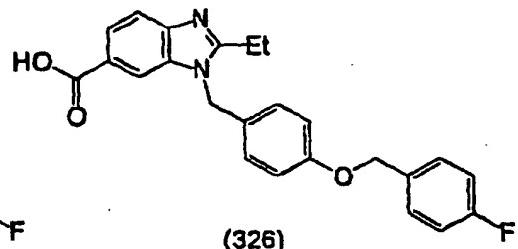
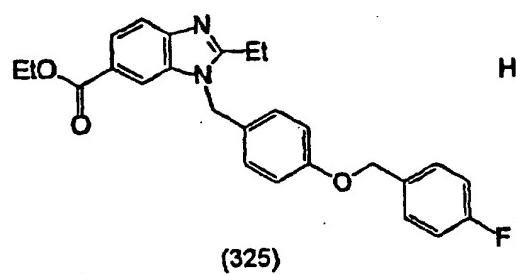
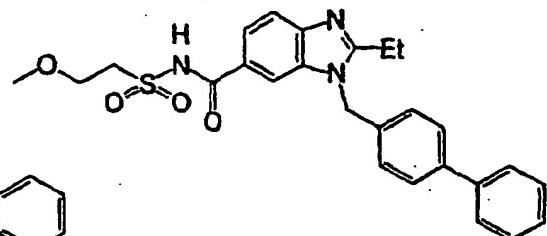
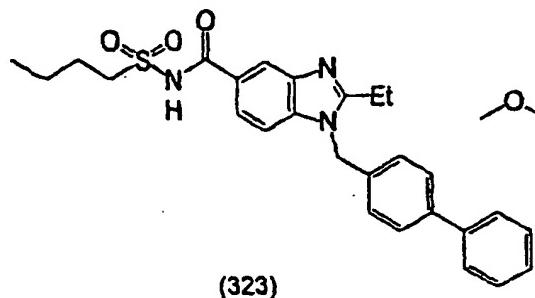


FIG. 49

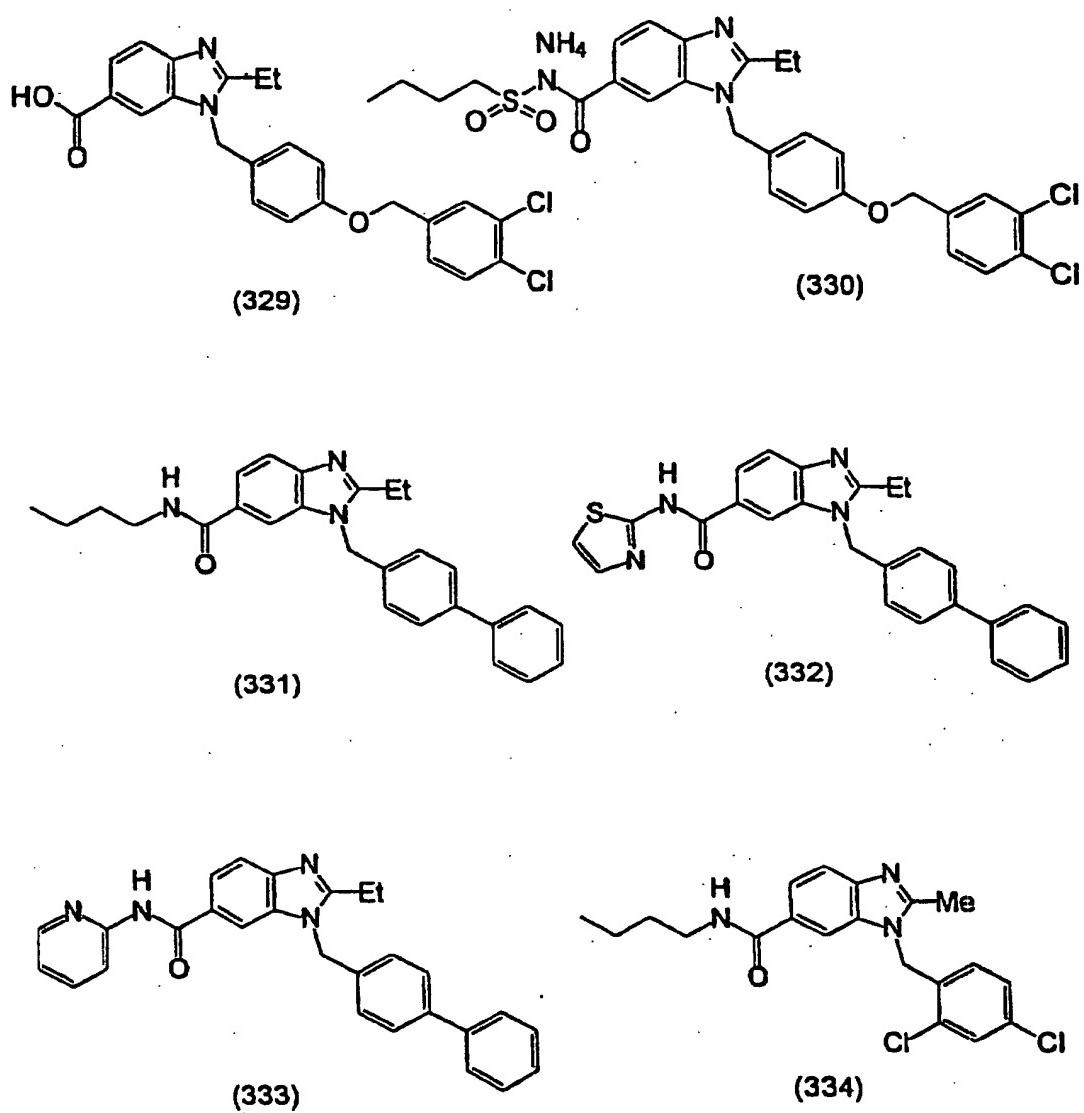


FIG. 50

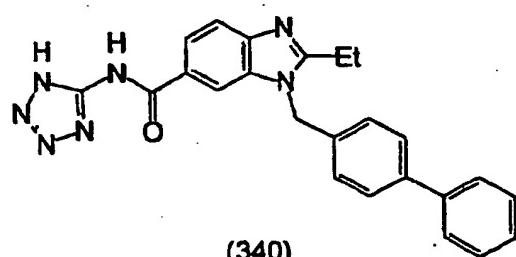
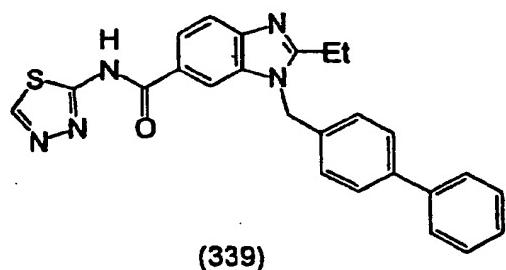
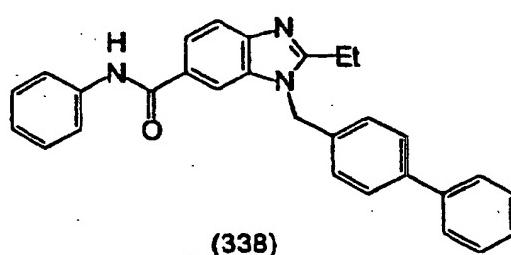
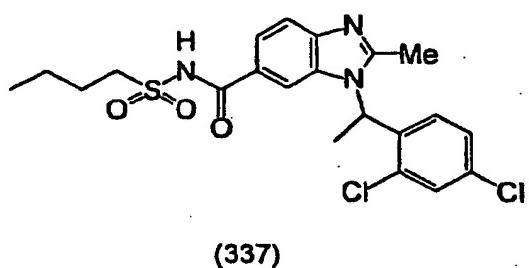
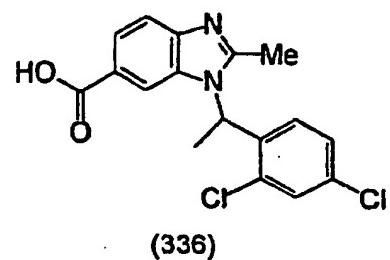
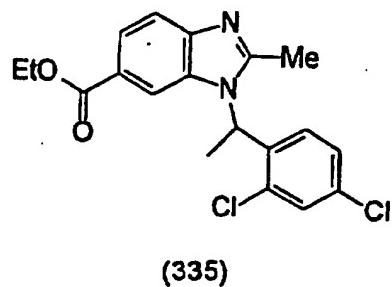


FIG. 51

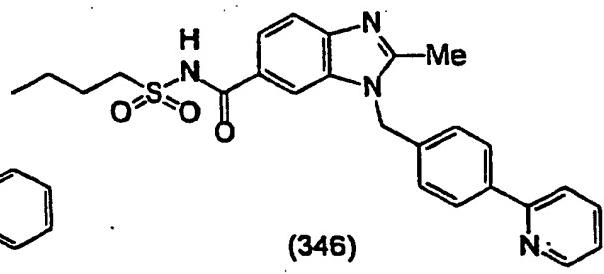
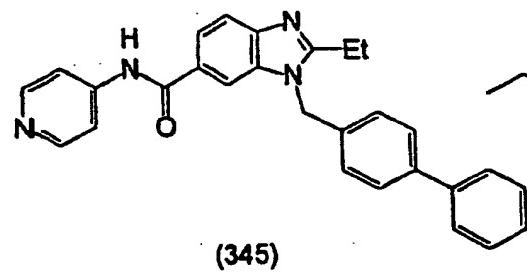
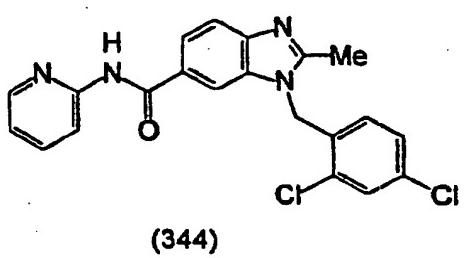
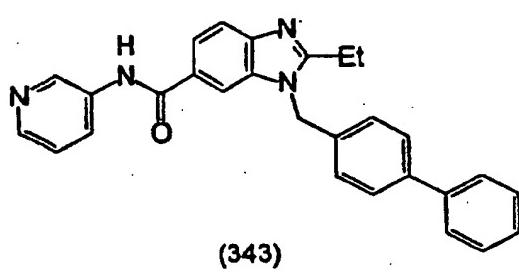
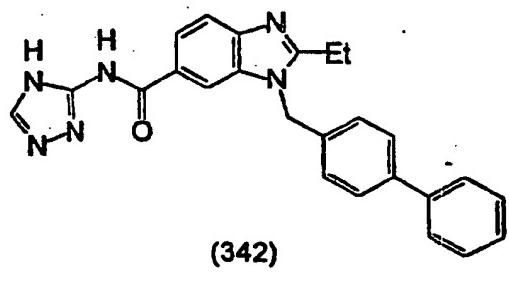
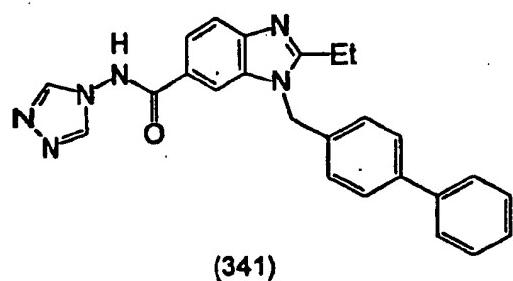
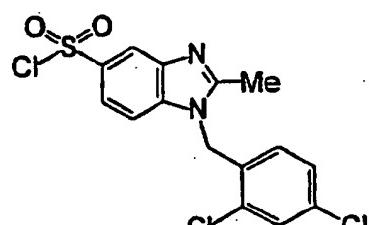
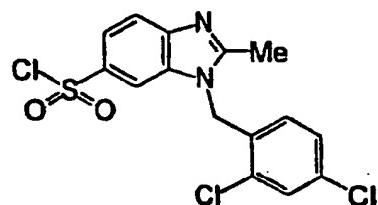


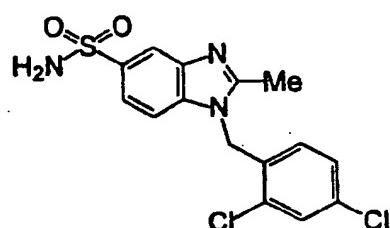
FIG. 52



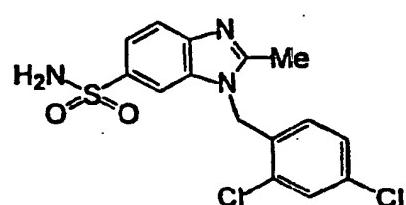
(347)



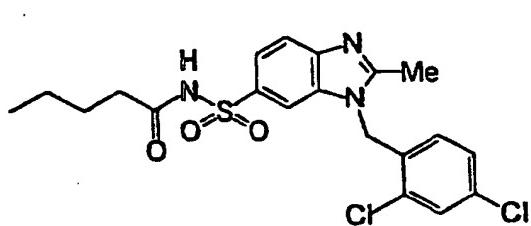
(348)



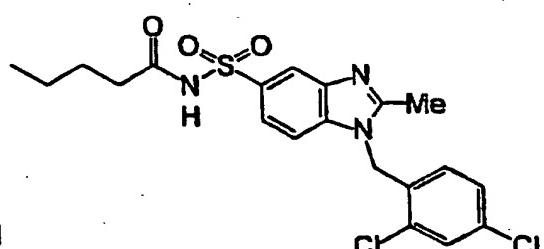
(349)



(350)

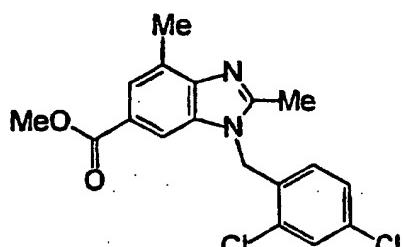


(351)

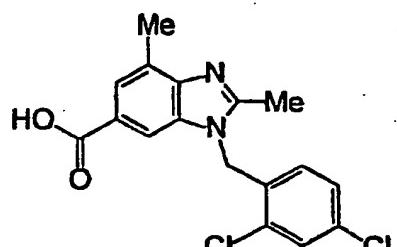


(352)

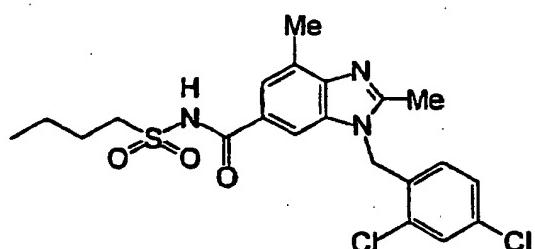
FIG. 53



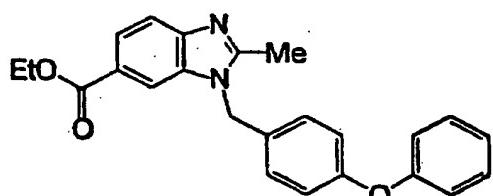
(353)



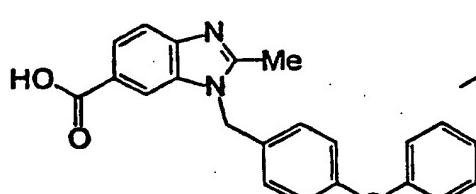
(354)



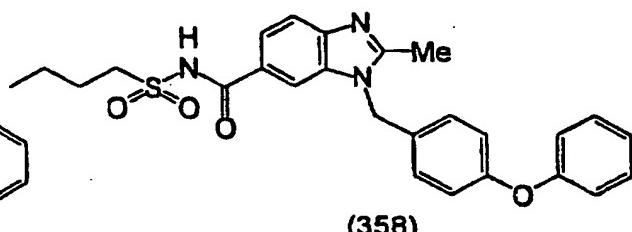
(355)



(356)

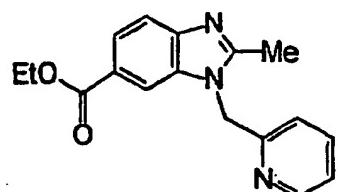


(357)

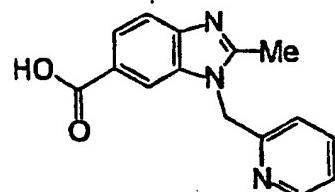


(358)

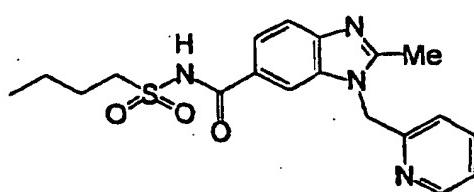
FIG. 54



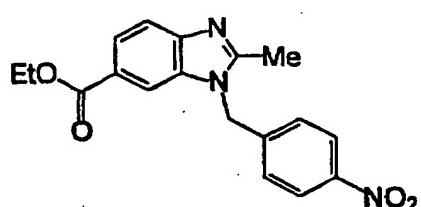
(359)



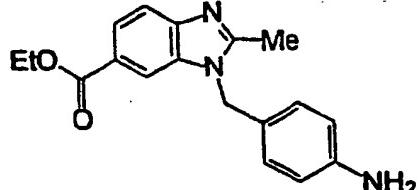
(360)



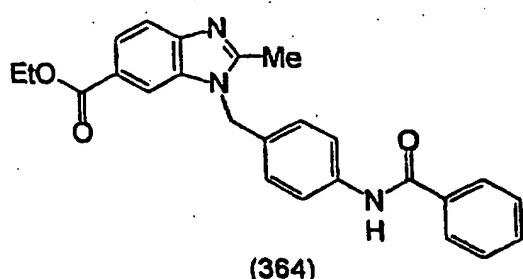
(361)



(362)



(363)



(364)

FIG. 55

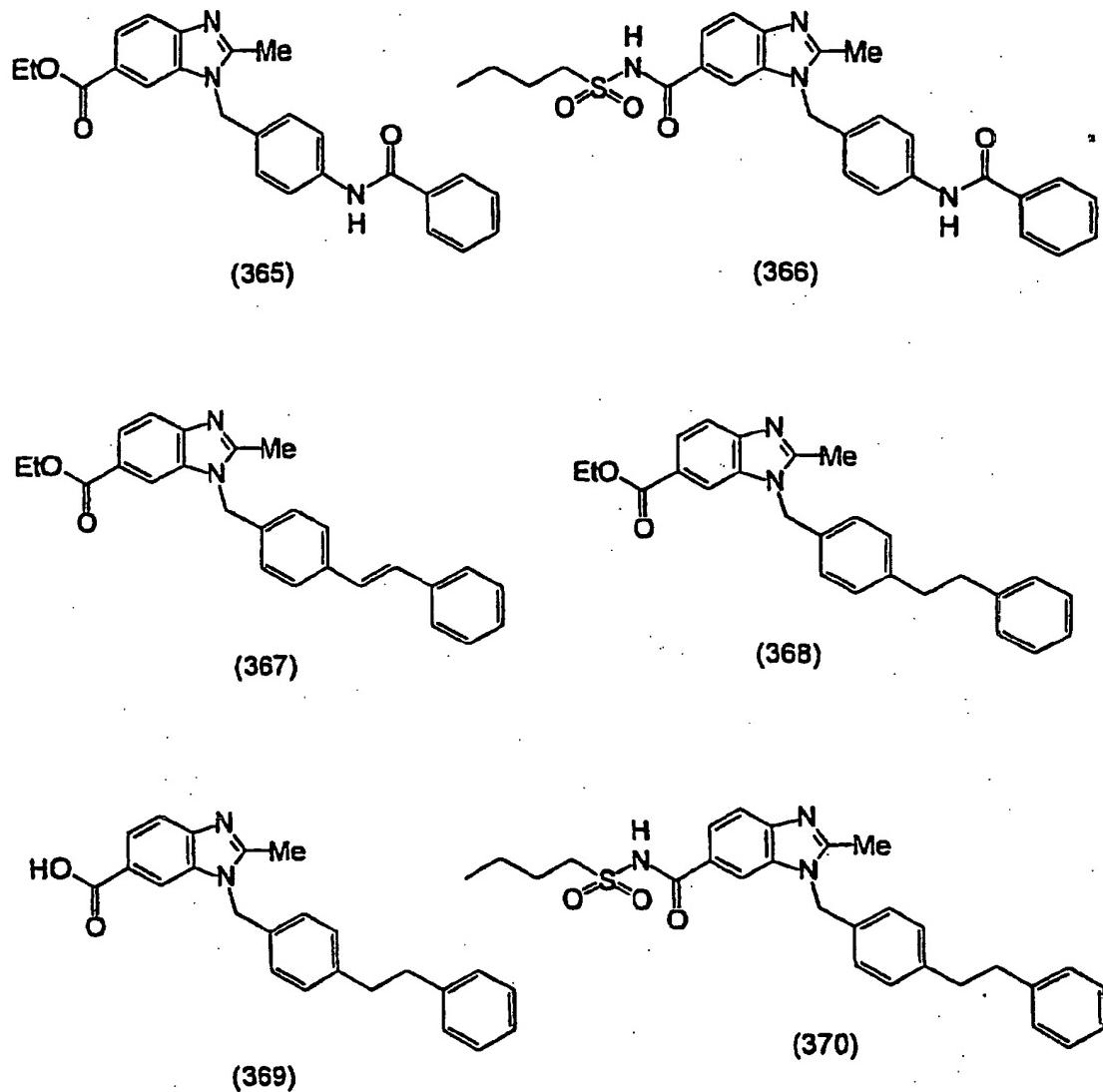


FIG. 56

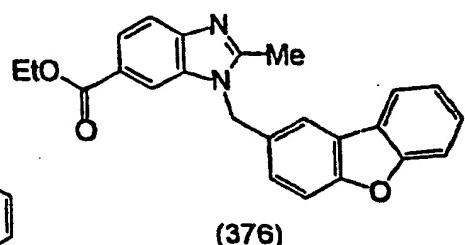
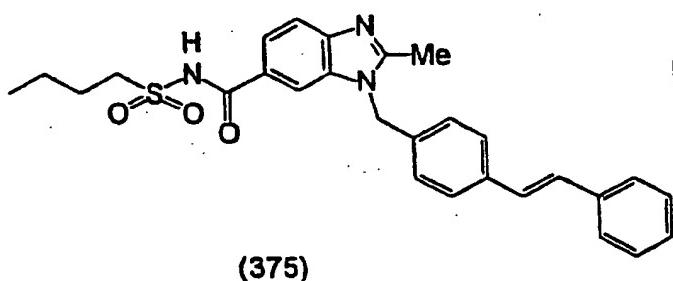
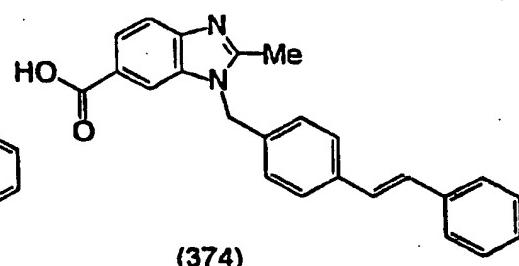
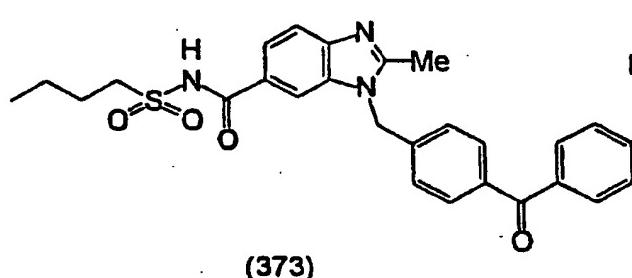
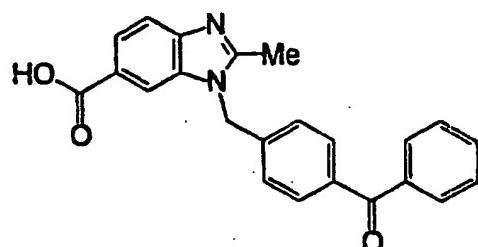
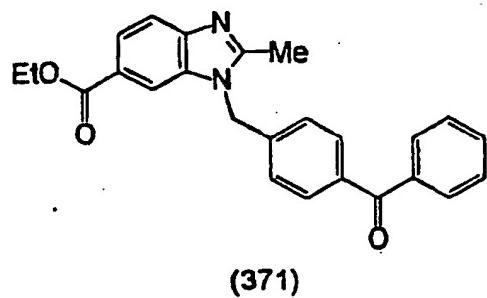
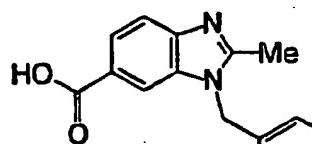
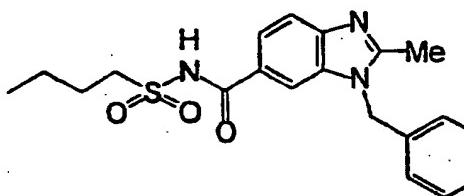


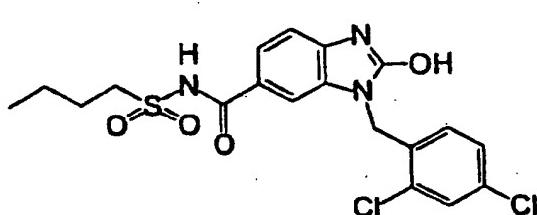
FIG. 57



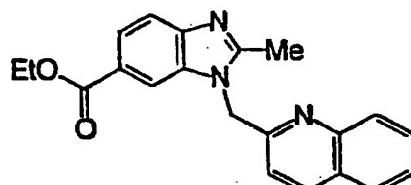
(377)



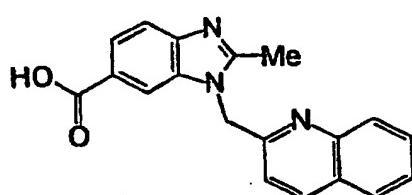
(378)



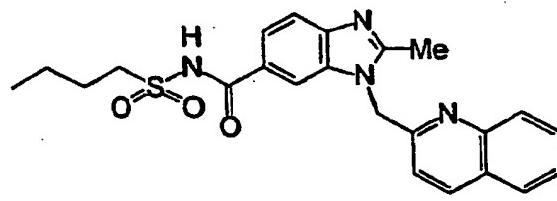
(379)



(380)



(381)



(382)

FIG. 58

